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Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses (Review)

Jayakody K, Gibson RC, Kumar A, Gunadasa S

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[Intervention Review]

Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses

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ABSTRACT

Background

Medication used for acute aggression in psychiatry must have rapid onset of effect, low frequency of administration and low levels of adverse effects. Zuclopenthixol acetate is said to have these properties.

Objectives

To estimate the clinical effects of zuclopenthixol acetate for the management of acute aggression or violence thought to be due to serious mental illnesses, in comparison to other drugs used to treat similar conditions.

Search methods

We searched the Cochrane Schizophrenia's Group Trials Register (July 2011). We supplemented this by citation searching and personal contact with authors and relevant pharmaceutical companies.

Selection criteria

All randomised clinical trials involving people thought to have serious mental illnesses comparing zuclopenthixol acetate with other drugs.

Data collection and analysis

Two review authors extracted and cross-checked data independently. We calculated fixed-effect relative risks (RR) and 95% confidence intervals (CI) for dichotomous data. We analysed by intention-to-treat. We used mean differences (MD) for continuous variables.

Main results

We found no data for the primary outcome, tranquillisation. Compared with haloperidol, zuclopenthixol acetate was no more sedating at two hours (n = 40, 1 RCT, RR 0.60, 95% CI 0.27 to 1.34). People given zuclopenthixol acetate were not at reduced risk of being given supplementary antipsychotics (n = 134, 3 RCTs, RR 1.49, 95% CI 0.97 to 2.30) although additional use of benzodiazepines was less (n = 50, 1 RCT, RR 0.03, 95% CI 0.00 to 0.47). People given zuclopenthixol acetate had fewer injections over seven days compared with those allocated to haloperidol IM (n = 70, 1 RCT, RR 0.39, 95% CI 0.18 to 0.84, NNT 4, CI 3 to 14). We found no data on more episodes of aggression or harm to self or others. One trial (n = 148) reported no significant difference in adverse effects for people receiving zuclopenthixol acetate compared with those allocated haloperidol at one, three and six days (RR 0.74, 95% CI 0.43 to 1.27). Compared with haloperidol or clotiapine, people allocated zuclopenthixol did not seem to be at more risk of a range of movement disorders (< 20%). Three studies found no difference in the proportion of people getting blurred vision/dry mouth (n = 192, 2 RCTs, RR at 24 hours 0.90, 95% CI 0.48 to 1.70). Similarly, dizziness

was equally infrequent for those allocated zuclopenthixol acetate compared with haloperidol (n = 192, 2 RCTs, RR at 24 hours 1.15, 95% CI 0.46 to 2.88). There was no difference between treatments for leaving the study before completion (n = 522, RR 0.85, 95% CI 0.31 to 2.31). One study reported no difference in adverse effects and outcome scores, when high dose (50-100 mg/injection) zuclopenthixol acetate was compared with low dose (25-50 mg/injection) zuclopenthixol acetate.

Authors' conclusions

Recommendations on the use of zuclopenthixol acetate for the management of psychiatric emergencies in preference to 'standard' treatment have to be viewed with caution. Most of the small trials present important methodological flaws and findings are poorly reported. This review did not find any suggestion that zuclopenthixol acetate is more or less effective in controlling aggressive acute psychosis, or in preventing adverse effects than intramuscular haloperidol, and neither seemed to have a rapid onset of action. Use of zuclopenthixol acetate may result in less numerous coercive injections and low doses of the drug may be as effective as higher doses. Well-conducted pragmatic randomised controlled trials are needed.

PLAIN LANGUAGE SUMMARY

Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses

People with schizophrenia or other mental health problems often hear disturbing voices or see distressing things (which are called delusions, hallucinations and psychosis). Such experiences can be frightening and may lead people to be aggressive or show violent behaviour toward themselves or other people. Tranquilising drugs are medications that help people to sleep or calm down, and help stop aggressive or disorganised behaviour. An antipsychotic effect is also desirable to help stop the delusions and hallucinations. Tranquillisers should not have to be used often and also have few unwanted side-effects, such as pain at the injection site or uncontrolled shaking of the head and hands. Zuclopenthixol acetate is said to possess all these properties.

Zuclopenthixol acetate is given by an injection and has an effect that lasts for about two to three days. This review looks at zuclopenthixol acetate for managing aggression or violence. The review did not find any evidence that zuclopenthixol acetate is more or less effective in helping to control aggression or violence, or in preventing unwanted side-effects than other drugs (such as haloperidol, chlorpromazine, clothiapine). It did not seem to work quickly and/or be rapid in calming people down.

Zuclopenthixol acetate may result in less forced injections (where restraint of the patient is needed to enable treatment). Low doses of the drug (as low as 25 mg) may be just as good and effective as higher doses (up to 100 mg).

Overall the review found limited information for claims made to support the use of this drug (for example: that it rapidly calms or sedates people; or that it is better than other drugs in emergency situations). Recommendations on the use of zuclopenthixol acetate for aggressive or violent behaviour therefore have to be viewed with caution.

Evidence is very far from good and convincing. Most of the research on the subject is small in size, with few participants, of short duration and data poorly reported in the individual studies. But it does point to zuclopenthixol acetate being helpful for managing very disturbed people. In comparison to other drugs it is not any worse than others. Moreover, the whole area on the management of very disturbed people is under-researched and more research is necessary.

This Plain Language Summary has been written by a consumer: Benjamin Gray, Service User and Service User Expert, Rethink Mental Illness, Email: ben.gray@rethink.org .

Summary of findings for the main comparison. ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE for acute schizophrenia and similar serious mental illnesses

ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE for acute schizophrenia and similar serious mental illnesses

Patient or population: patients with acute schizophrenia and similar serious mental illnesses
Settings:
Intervention: ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE				
Sedation/tranquillisation: Not sedated - at four hours Follow-up: 9 days	**Low[1]**		**RR 0.74** (0.54 to 1)	40 (1 study)	⊕⊕⊝⊝ **low**[2,3]	
	800 per 1000	**592 per 1000** (432 to 800)				
	Moderate[1]					
	900 per 1000	**666 per 1000** (486 to 900)				
	High[1]					
	1000 per 1000	**740 per 1000** (540 to 1000)				
Global state: 1. Requiring supplementary medication - antipsychotics Follow-up: 3-9 days	**Low[1]**		**RR 1.49** (0.97 to 2.3)	134 (3 studies)	⊕⊕⊝⊝ **low**[2,3]	
	100 per 1000	**149 per 1000** (97 to 230)				
	Moderate[1]					
	300 per 1000	**447 per 1000** (291 to 690)				

	High[1]				
	500 per 1000	**745 per 1000** (485 to 1000)			
Global state: 2. Requiring 3 or more injections - over 7 days Follow-up: 7 days	**Low[1]**		**RR 0.39** (0.18 to 0.84)	70 (1 study)	⊕⊕⊖⊖ **low**[2,3]
	200 per 1000	**78 per 1000** (36 to 168)			
	Moderate[1]				
	500 per 1000	**195 per 1000** (90 to 420)			
	High[1]				
	800 per 1000	**312 per 1000** (144 to 672)			
Mental state: 1. No important improvement Follow-up: 6-9 days	**Low[1]**		**RR 0.86** (0.39 to 1.86)	188 (2 studies)	⊕⊕⊖⊖ **low**[2,3]
	100 per 1000	**86 per 1000** (39 to 186)			
	Moderate[1]				
	150 per 1000	**129 per 1000** (58 to 279)			
	High[1]				
	200 per 1000	**172 per 1000** (78 to 372)			
Adverse effects: Movement disorders - dystonia (spasmodic postural disorder) - by 24 hours	**Low[1]**		**RR 0.68** (0.34 to 1.36)	242 (3 studies)	⊕⊕⊖⊖ **low**[2,3]
	50 per 1000	**34 per 1000** (17 to 68)			
	Moderate[1]				
	100 per 1000	**68 per 1000**			

		(34 to 136)
High[1]		
150 per 1000		**102 per 1000** (51 to 204)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Moderate risk similar to that in control group.
[2] Risk of bias: rated 'serious' - allocation unclear.
[3] Imprecision: rated 'serious' - small trial/s, wide confidence intervals.

Summary of findings 2. ZUCLOPENTHIXOL ACETATE (HIGH DOSE) compared to ZUCLOPENTHIXOL ACETATE (LOW DOSE) for acute schizophrenia and similar serious mental illnesses

ZUCLOPENTHIXOL ACETATE (HIGH DOSE) compared to ZUCLOPENTHIXOL ACETATE (LOW DOSE) for acute schizophrenia and similar serious mental illnesses

Patient or population: patients with acute schizophrenia and similar serious mental illnesses
Settings:
Intervention: ZUCLOPENTHIXOL ACETATE (HIGH DOSE)
Comparison: ZUCLOPENTHIXOL ACETATE (LOW DOSE)

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	ZUCLOPENTHIXOL ACETATE (LOW DOSE)	**ZUCLOPENTHIXOL ACETATE (HIGH DOSE)**				
Sedation/tranquillisation: Not sedated - at two hours Follow-up: 6 days	See comment	See comment	Not estimable	0 (0)	See comment	No studies reported this outcome.

Global state: 1. Requiring supplementary medication - antipsychotics Follow-up: 6 days	See comment	See comment	Not estimable	0 (0)	See comment	No studies reported this outcome.
Global state: 2. Requiring 3 or more injections - over 7 days Follow-up: 6 days	See comment	See comment	Not estimable	0 (0)	See comment	No studies reported this outcome.
Mental state: 1. Not markedly improved (BPRS, < 60% decrease in BPRS score) Follow-up: 6 days	**Low**		**RR 1** (0.51 to 1.95)	30 (1 study)	⊕⊕⊖⊖ **low**[1,2]	
	300 per 1000	**300 per 1000** (153 to 585)				
	Moderate					
	500 per 1000	**500 per 1000** (255 to 975)				
	High					
	700 per 1000	**700 per 1000** (357 to 1000)				
Mental state: 2. Not improved (BPRS, < 30% decrease in BPRS score) Follow-up: 6 days	**Low**		**RR 0.6** (0.17 to 2.07)	30 (1 study)	⊕⊕⊖⊖ **low**[1,2]	
	100 per 1000	**60 per 1000** (17 to 207)				
	Moderate					
	300 per 1000	**180 per 1000** (51 to 621)				
	High					
	500 per 1000	**300 per 1000** (85 to 1000)				
Adverse effects: 1. Extrapyramidal side effects (TESS) Follow-up: 6 days	**Low**[3]		**RR 2.33** (0.74 to 7.35)	30 (1 study)	⊕⊕⊖⊖ **low**[1,2]	
	100 per 1000	**233 per 1000** (74 to 735)				

Moderate[3]	
200 per 1000	**466 per 1000** (148 to 1000)
High[3]	
300 per 1000	**699 per 1000** (222 to 1000)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Risk of bias: rated 'serious' - allocation unclear.
[2] Imprecision: rated 'serious' - small trial, wide confidence intervals.
[3] Moderate risk similar to that in control group.

BACKGROUND

Description of the condition

Schizophrenia is a mental illness with an annual incidence of 0.16 to 0.54 per 1000 population using current diagnostic criteria. The prevalence of this illness is about 1.4 to 4.61 per 1000 population at risk (Jablensky 1992; Jablensky 2003). The symptoms include psychosis, apathy, social withdrawal and cognitive impairment which lead to disturbances in social and occupational functioning, and self care (Mueser 2004). It often runs a chronic course with acute exacerbations and often partial remissions. Antipsychotics are often used as the primary choice of medications for treatment of schizophrenia and related conditions which can bring about considerable improvements with a reduction in psychotic symptoms and prevention of future relapses (Kane 1993).

Description of the intervention

Originally clopenthixol was a mixture of two chemical isomers: *cis* (*Z*) - and *trans* (*E*) -clopenthixol. The *cis* (*Z*) -isomer, called zuclopenthixol, is the active form. It has high affinity for both dopamine D_1 and D_2 receptors. This compound is mainly produced in three preparations; zuclopenthixol acetate: zuclopenthixol dihydrochloride (zuclopenthixol hydrochloride) and zuclopenthixol decanoate.

Zuclopenthixol acetate (cis (Z) -4- [3- (2-chlorothioxanthen-9-ylidene) propyl] -l-piperazineethanol acetate) is an intramuscular depot injection with a duration of two to three days action. This acetate preparation was synthesised in the mid-1980s and the new formulation for intramuscular use was obtained by dissolving zuclopenthixol acetate in vegetable oil (Baastrup 1993). It has a product license for management of acute exacerbation of serious mental illnesses in doses of 50-150 mg (Lundbeck 1987; Lundbeck 2011). The chemical formula for zuclopenthixol acetate is $C_{24}H_{27}ClN_2O_2S$ with a molecular weight of 443.04 g/mol. The other two preparations, zuclopenthixol dihydrochloride is relatively short acting and zuclopenthixol decanoate (another intramuscular depot injection) acts for weeks (Coutinho 2000b).

How the intervention might work

People with schizophrenia or other psychotic illnesses can have delusions or hallucinations that may lead them to be aggressive or violent to themselves or others (Atakan 1997; Travin 1990). In these situations, carers have several ways to bring the situation under control (Abdullahi 1993; Atakan 1997). Medication used in this context should have a swift onset of effect. Tranquillisation, or at least initial sedation in order to quell aggressive or disorganised behaviour is essential, but also an antipsychotic effect is desirable. The tranquillising drug should also have a low frequency of administration and low levels of adverse effects, such as movement disorders or pain at the injection site. Zuclopenthixol acetate is said to possess all these properties (Baastrup 1993). Open and uncontrolled clinical studies have suggested that this preparation is at least as effective as oral or intramuscular haloperidol for controlling the symptoms of acutely psychotic people. These studies also reported that zuclopenthixol acetate provided early sedation, low levels of neurological effects and other adverse effects (Amisden 1986; Amisden 1987; Balant 1989; Chakravarti 1990; Lowert 1989; Predescu 1991; Romain 1996; Schlosberg 1991; Tan 1993). Zuclopenthixol acetate has been recommended for the treatment of mental health emergencies in hospital (Atakan 1997). It has also been suggested that by using reduced doses of zuclopenthixol acetate, people in the community experiencing acute exacerbation of symptoms will require less hospitalisation (Abdullahi 1993).

Why it is important to do this review

This review was last updated in 2003 (Gibson 2004). It found no data on tranquillisation effect, dose dependent effect and economic outcomes of zuclopenthixol acetate. It seems for many psychiatrists, zuclopenthixol acetate is the parenteral drug of choice for rapid tranquillisation in an inpatient setting (Simpson 1996). There have been new studies published since 2003 with regard to this medication and hence a new update is needed and this is one of a series of linked reviews (Table 1).

OBJECTIVES

1. To estimate the effects of zuclopenthixol acetate when compared with either 'standard' or 'non-standard' care in controlling disturbed behaviour and improving mental state in those with similar mental illness.

2. To investigate whether zuclopenthixol acetate in low dose (25-50 mg/injection) has particular advantage over high dose (50-100 mg/injection) when compared with other neuroleptics for people with schizophrenia and other similar mental illnesses.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised clinical trials.

Types of participants

People with schizophrenia or similar psychotic illness, irrespective of age or sex. We excluded those with dementing illnesses, depression and substance induced mental illnesses.

Types of interventions

1. Zuclopenthixol acetate

Any dose given as an intramuscular injection.

2. Standard medication

Drug treatments that fit with normal 'custom and practice'. This may involve increasing the dose of usual medication or addition of a further 'conventional' antipsychotic. We expected standard care to be given orally or by deep intramuscular injection.

3. Non-standard medication

Drug treatments which are undergoing trials (new type of intervention).

Types of outcome measures

Zuclopenthixol acetate has been suggested to be of use over periods of time that are very short in relation to the duration of illnesses such as schizophrenia. For outcomes, with the exception of sedation, this review defines short term as up to six hours,

medium term from 7-36 hours, and long term greater than 36 hours. For the outcome of tranquillisation and sedation, where immediate onset of effect is desirable in an emergency situation, the time of evaluation was assessed at two hours, four hours, eight hours and 24 hours after the first dose.

Primary outcomes

This review has had update searches run in 2003 and 2011. Part of the update process of Cochrane schizophrenia reviews are a refinement of methods and this includes a stipulation of outcomes of primary interest. This was not undertaken for the first versions of this review (Coutinho 2000a; Fenton 1997; Fenton 2000; Fenton 2001) but is now routine practice for protocols and reviews relevant to the care of people with schizophrenia. Choosing the primary outcomes helps focus discussion and limits sensitivity analyses. We were confronted with the problem of the likely inclusion of bias by our foreknowledge of outcome data. In the 2003 update, two researchers blind to the data, Suki Kaur and Julie Kitcheman were asked to choose the primary outcomes from the full list of outcomes as an attempt to avoid bias.

The primary outcomes are as follows;

1 Tranquillisation (feeling of calmness and/or calm, non-sedated behaviour)

2. Sedation (sleepiness and drowsiness)

2. Global state

2.1 Clinically significant changes in global state - as defined by each of the studies
2.2 Clinically relevant outcome/s such as 'Requiring supplementary medication' or 'Requiring more injections'
2.3 Use of seclusion/restraints
2.4 Episodes of aggression/violence
2.5 Episodes of self harm (including suicide)
2.6 Injury to others
2.7 Compulsory administrations of treatment
2.8 Medication compliance
2.9 Relapse
2.10 Clinically important improvement in self care, or degree of change in self care

3. Mental state

3.1 Clinically relevant outcome/s such as 'Important improvement' in general mental state
3.2 Clinically important reduction in severity of symptoms as defined by each study
3.3 Any reduction in severity of symptoms
3.4 Increase in symptoms
3.5 Degree of change in severity of symptoms

4. Adverse effects

4.1 Incidence of adverse effects, general and specific
4.2 Leaving the study early
4.3 Measured acceptability of treatment
4.4 Use of antiparkinson medication
4.5 Sudden and unexpected death

Secondary outcomes

5. Hospital and service outcomes

5.1 Hospitalisation of people in the community
5.2 Duration of hospital stay
5.3 Changes in hospital status (changes from informal care to formal detention in care, changes in level of observation by ward staff, use of secluded nursing environment)
5.4 Changes in services provided by community teams

6. Satisfaction with care

6.1 Recipients of care
6.2 Informal care givers
6.3 Professional carers

7. Economic outcomes

8. Summary of findings table

We used the GRADE approach to interpret findings (Schünemann 2008) and used GRADE profiler to import data from Review Manager to create a 'Summary of findings' tables. These tables provide outcome-specific information concerning; the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as important to patient-care and decision making. We selected the following main outcomes for inclusion in the summary of findings:

- Sedation/tranquillisation – clinically relevant outcome/s such as 'Sedated – by specified time period'.
- Global state – clinically relevant outcome/s such as 'Requiring supplementary medication' or 'Requiring more injections'.
- Mental state – clinically relevant outcome/s such as 'Important improvement'.
- Adverse effects – important problems such as 'Movement disorders – dystonia'.

Search methods for identification of studies

Electronic searches

For previous search terms please see Appendix 1

1. The search run in 2011

We searched the Cochrane Schizophrenia Group's Register in July 2011 with the phrase:

[((*Ciatyl* or *Cisordinol* or *Semi Prolongee* or *Acuphase* or *Clopixol-Acutard*) or (zuclopenthixol and (acetate* or (short and acting)))) in title, abstract or index terms of REFERENCE] or [(Zuclopenthixol acetate* in interventions of study]

The Schizophrenia Groups trials register is based on regular searches of BIOSIS Inside; CENTRAL; CINAHL; EMBASE; MEDLINE and PsychINFO; the handsearching of relevant journals and conference proceedings, and searches of several key grey literature sources.

Searching other resources

1. Handsearching

We also searched reference from the list of references in selected papers.

2. Requests for additional data

2.1 We sought unpublished data through sending a letter to the British Medical Journal (Coutinho 1997a).

2.2 We contacted the Medical Information Department of Lundbeck Limited which developed and manufactures the drug, for published and unpublished studies.

2.3 Where possible, we contacted authors of relevant studies for additional data.

Data collection and analysis

For the 2011 update, we have substantially updated the data collection and analysis section to reflect substantial updates in the Cochrane Schizophrenia Group's methodology and review layouts for Revman 5.1. For previous methods of data collection and analysis please see Appendix 2.

Selection of studies

KJ and AK independently inspected citations from the searches and identified relevant abstracts. Where disputes arose, the full report was acquired for more detailed scrutiny. If citations met inclusion criteria, we obtained full reports of the papers for more detailed inspection. A random 20% of reports were re-inspected by AK in order to ensure reliable selection. Where it was not possible to resolve disagreement by discussion, we attempted to contact the authors of the study for clarification.

Data extraction and management

1. Extraction

Review author KJ extracted data from all included studies. In addition, to ensure reliability, AK independently extracted data from a random sample of these studies, comprising 10% of the total. Again, any disagreement was discussed, decisions documented and, if necessary, authors of studies contacted for clarification. With remaining problems SG helped clarify issues and we documented these final decisions. Data presented only in graphs and figures were extracted whenever possible, but included only if two review authors independently had the same result. We attempted to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. If studies were multicentre, where possible, we extracted data relevant to each component centre separately.

2. Management

2.1 Forms

We extracted data onto standard forms.

2.2 Scale-derived data

We included continuous data from rating scales only if:
a. the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000); and
b. the measuring instrument has not been written or modified by one of the trialists for that particular trial.

Ideally, the measuring instrument should either be a self-report or completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly, and in Description of studies we noted if this was the case or not.

2.3 Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. On the other hand, calculation of change needs two assessments (baseline and endpoint) which can be difficult in unstable and difficult to measure conditions such as schizophrenia. We decided primarily to use endpoint data, and only use change data if the former were not available. We combined endpoint and change data in the analysis as we used mean differences (MD) rather than standardised mean differences (SMD) throughout (Higgins 2011).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we aimed to apply the following standards to all data before inclusion: a) standard deviations (SDs) and means are reported in the paper or obtainable from the authors; b) when a scale starts from the finite number zero, the SD, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution, (Altman 1996); c) if a scale started from a positive value (such as the Positive and Negative Syndrome Scale (PANSS) which can have values from 30 to 210), the calculation described above was modified to take the scale starting point into account. In these cases skew is present if 2 SD > (S-S min), where S is the mean score and S min is the minimum score. Endpoint scores on scales often have a finite start and end point and these rules can be applied. When continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. We entered skewed data from studies of less than 200 participants in additional tables rather than into an analysis. Skewed data pose less of a problem when looking at mean if the sample size is large, we entered such data into the syntheses.

2.5 Common measure

To facilitate comparison between trials, we intended to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we made efforts to convert outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962) or the PANSS (Kay 1986), this could be considered as a clinically significant response (Leucht 2005; Leucht 2005a). If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

2.7 Direction of graphs

Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for zuclopenthixol acetate. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not

improved') we reported data where the left of the line indicates an unfavourable outcome. This was noted in the relevant graphs.

Assessment of risk of bias in included studies

Again, KJ and AK worked independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to assess trial quality. This set of criteria is based on evidence of associations between an overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

If the raters disagreed, the final rating was made by consensus, with the involvement of another member of the review group. Where inadequate details of randomisation and other characteristics of trials were provided, we contacted the authors of the studies in order to obtain further information. We reported non-concurrence in quality assessment, but if disputes arose as to which category a trial was to be allocated, again, resolution was made by discussion.

The level of risk of bias was noted in both the text of the review and in the included study tables below.

Measures of treatment effect

1. Binary data

For binary outcomes, we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). For statistically significant results, we had planned to calculate the number needed to treat to provide benefit/to induce harm statistic (NNTB/H), and its 95% confidence interval (CI) using Visual Rx (http: //www.nntonline.net/) taking account of the event rate in the control group. This, however, has been superseded by Summary of findings for the main comparison and the calculations therein.

2. Continuous data

For continuous outcomes, we estimated mean difference (MD) between groups. We would prefer not to have to calculate effect size measures [standardised mean difference (SMD)]. However, if scales of very considerable similarity had been used, we would have presumed there was a small difference in measurement, and we would have calculated effect size and transformed the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering is not accounted for in primary studies, we presented data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation coefficients for their clustered data and to adjust for this by using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we presented these data as if from a non-cluster randomised study, but adjusted for the clustering effect.

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intra-class correlation coefficient (ICC) [Design effect = 1+ (m-1) *ICC] (Donner 2002). If the ICC was not reported, it was assumed to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed taking into account intra-class correlation coefficients and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. It occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, on entry to the second phase the participants can differ systematically from their initial state despite a wash-out phase. For the same reason cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in severe mental illness, we only used the data of the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involved more than two treatment arms, if relevant, the additional treatment arms were presented in comparisons. If data were binary, we simply added and combined them within the two-by-two table. If data were continuous, we combined data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions*. Where the additional treatment arms were not relevant, we did not use these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss to follow-up, data must lose credibility (Xia 2009). We chose that, for any particular outcome, should more than 50% of data be unaccounted for, we did not present these data or use them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we marked such data with (*) to indicate that such a result may well be prone to bias.

2. Binary

In the case where attrition for a binary outcome was between 0% and 50% and where these data were not clearly described, we presented data on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis). Those leaving the study early were all assumed to have the same rates of negative outcome as those who completed, with the exception of the outcome of death and adverse effects. For these outcomes the rate of those who stayed in the study - in that particular arm of the trial - were used for those who did not. We undertook a sensitivity analysis to test how prone

the primary outcomes were to change when 'completer' data only were compared with the intention-to-treat analysis using the above assumptions.

3. Continuous

3.1 Attrition

In the case where attrition for a continuous outcome was between 0% and 50% and completer-only data were reported, we presented and used these data.

3.2 Standard deviations

If standard deviations (SDs) were not reported, we first tried to obtain the missing values from the authors. If not available, where there are missing measures of variance for continuous data, but an exact standard error (SE) and confidence intervals (CIs) available for group means, and either a 'P' value or 't' value are available for differences in mean, we can calculate them according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011): When only the SE is reported, SDs are calculated by the formula SD = SE * square root (n). Chapters 7.7.3 and 16.1.3 (Higgins 2011) present detailed formulae for estimating SDs from P values, t or F values, CIs, ranges or other statistics. If these formulae did not apply, we calculated the SDs according to a validated imputation method which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study' s outcome and thus to lose information. We nevertheless examined the validity of the imputations in a sensitivity analysis excluding imputed values.

3.3 Last observation carried forward

We anticipated that in some studies the method of last observation carried forward (LOCF) would be employed within the study report. As with all methods of imputation to deal with missing data, LOCF introduces uncertainty about the reliability of the results (Leucht 2007). Therefore, where LOCF data were used in the trial, if less than 50% of the data had been assumed, we presented these data and indicated that they were the product of LOCF assumptions.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We simply inspected all studies for clearly outlying people or situations which we had not predicted would arise. When such situations or participant groups arose, these were fully discussed.

2. Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We simply inspected all studies for clearly outlying methods which we had not predicted would arise. When such methodological outliers arose, these were fully discussed.

3. Statistical heterogeneity

3.1 Visual inspection

We visually inspected graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2 statistic

Heterogeneity between studies was investigated by considering the I^2 method alongside the Chi^2 'P' value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. 'P' value from Chi^2 test, or a confidence interval for I^2). An I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic, was interpreted as evidence of substantial levels of heterogeneity (Section 9.5.2 - Higgins 2011). When substantial levels of heterogeneity were found in the primary outcome, we explored reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Section 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We did not use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar sizes. In other cases, where funnel plots were possible, we sought statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model. It puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect these studies can either inflate or deflate the effect size. We chose the fixed-effect model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroups

Where data permitted, seven such sub-groupings were pre-specified, recognising that data may be too sparse to undertake all of them.

i. Rigorous versus looser criteria for diagnosing schizophrenia

ii. Published versus unpublished trials

iii. High quality studies versus others

iv. Acute versus non-acute symptoms

v. Oral versus intramuscular antipsychotic

vi. Violent versus not violent behaviour

vii. Reduced dosage zuclopenthixol acetate versus standard dosage

2. Investigation of heterogeneity

If inconsistency was high, this was reported. Firstly, we investigated whether the data had been entered correctly. Secondly, if data were

correct, the graph was visually inspected, and outlying studies were successively removed to see if heterogeneity was restored. For this review, we decided that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, data were presented. If not, data were not pooled and issues were discussed. We know of no supporting research for this 10% cut-off but are investigating use of prediction intervals as an alternative to this unsatisfactory state.

Sensitivity analysis

1. Implication of randomisation

We aimed to include trials in a sensitivity analysis if they were described in some way as to imply randomisation. For the primary outcomes, we included these studies and if there was no substantive difference when the implied randomised studies were added to those with better description of randomisation, then all data were employed from these studies.

2. Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up (see Dealing with missing data), we compared the findings of the primary outcomes when we used our assumption compared with completer data only. If there was a substantial difference, we reported results and discussed them but continued to employ our assumption.

Where assumptions had to be made regarding missing SDs data (see Dealing with missing data), we compared the findings on primary outcomes when we used our assumption compared with complete data only. A sensitivity analysis was undertaken testing how prone results were to change when 'completer' data only were compared with the imputed data using the above assumption. If there was a substantial difference, we reported results and discussed them but continued to employ our assumption.

3. Risk of bias

We analysed the effects of excluding trials that were judged to be at high risk of bias across one or more of the domains of randomisation (implied as randomised with no further details available), allocation concealment, blinding and outcome reporting for the meta-analysis of the primary outcome. If the exclusion of trials at high risk of bias did not substantially alter the direction of effect or the precision of the effect estimates, then we included the data from these trials in the analysis

4. Imputed values

We also undertook a sensitivity analysis to assess the effects of including data from trials where we used imputed values for ICC in calculating the design effect in cluster randomised trials.

If substantial differences were noted in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we did not pool data from the excluded trials with the other trials contributing to the outcome, but presented them separately

5. Fixed and random effects

All data were synthesised using a fixed-effect model. However, we re-analysed the data using a random-effects model to see if this made a substantial difference. If it did and results became more consistent, falling below 75% in the estimate, we added the studies to the main body of trials. If using the random-effects model did not make a difference and inconsistency remained high, data were not summated, but were presented separately and reasons for heterogeneity investigated (see Data synthesis).

RESULTS

Description of studies

Please see Characteristics of included studies and Characteristics of excluded studies.

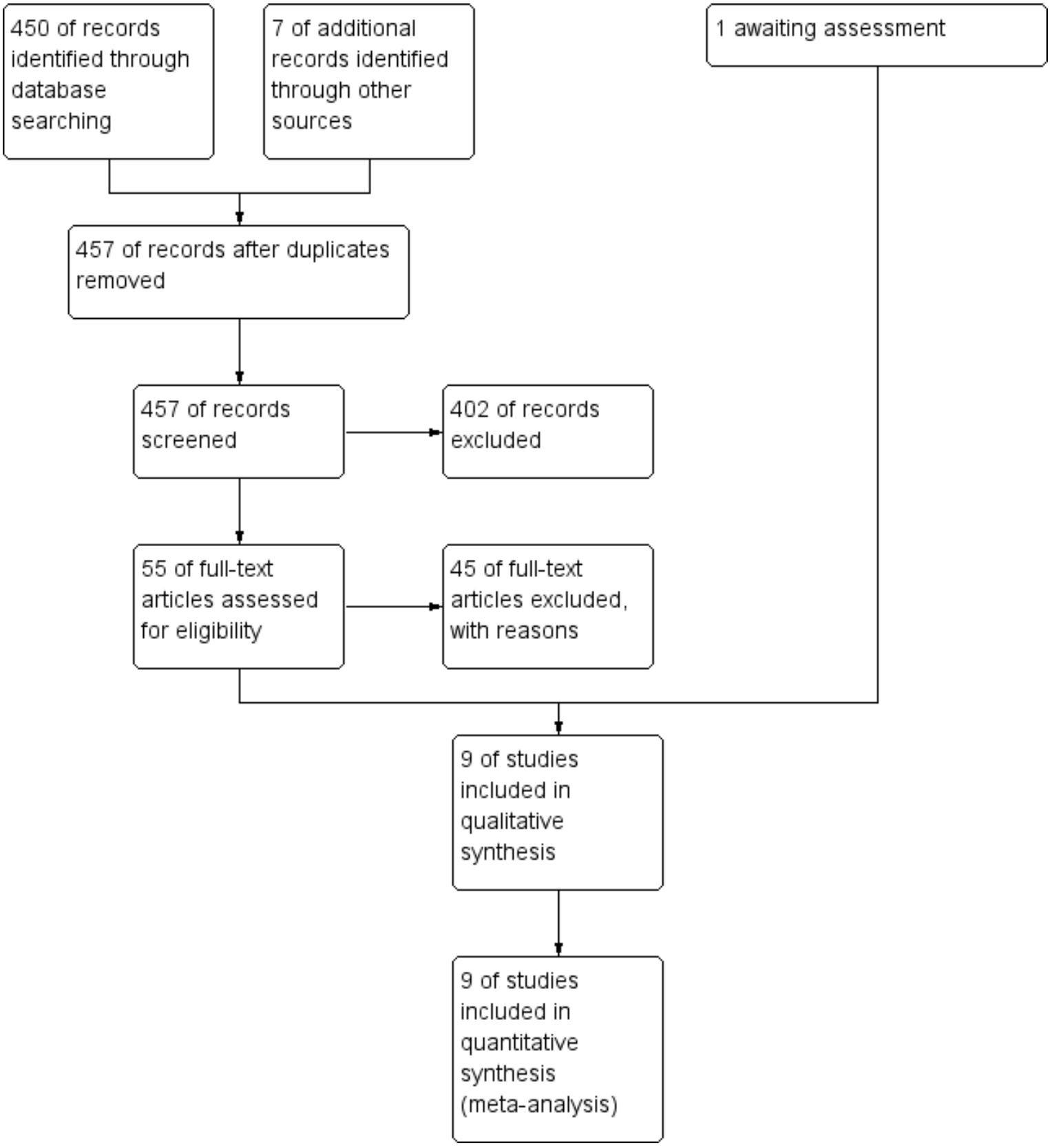
Results of the search

We found 392 citations using the search strategy. Thirty-six related to zuclopenthixol acetate but only 10 referred controlled clinical trials (four published in journals, five in abstracts of scientific meetings and one awaiting publication). Lundbeck kindly provided an additional study (France 1988) that had not been identified in any other way. For the first version of this review, the authors of one study awaiting publication (South Africa 1997) kindly provided data. This is now fully published. Publishing an appeal in the British Medical Journal (Coutinho 1997a) identified no further studies. From this search for the first version of the review, we identified six different studies from all sources of citations, and could include five.

For the 2003 search, 53 citations were found using the search strategy. We identified five more studies from references bringing the total to 58 but we could only include three in the update. The reliability of selection was high. Review authors agreed on the categorisation of 92.5% of the studies. In each case of disagreement, one review author had rated the study as 'for further evaluation'. In each of these cases, following further evaluation, we reached agreement on whether a study should be included or not.

For the 2011 search, five more studies were considered but only one (China 1997) was included and one is awaiting assessment (Lamure 2003). Overall study selection is shown in Figure 1.

Figure 1. Study flow diagram - 2011 update.



Included studies

We included nine studies in the quantitative meta-analysis (Bahrain 1996: Canada 1994: China 1997: France 1988: Malaysia 1998: Nordic 1993: South Africa 1996: South Africa 1997: Thailand 2002).

1. Duration

All studies were short, ranging from three days (Malaysia 1998) to four weeks duration (South Africa 1997). Most were six days long (China 1997; Bahrain 1996; France 1988; Nordic 1993; South Africa 1996).

2. Participants

All included studies focused on people who were 'acutely ill', even if they had suffered from serious mental illness for a long period of time. All but one included people of both sexes, with ages ranging from 18-65 years old and psychoses such as schizophrenia or mania. South Africa 1997 included some people with substance-induced psychotic disorder. Data from this sub-group were not included in this review. It was possible to use limited data relating only to those with schizophrenia (seeTypes of participants).

3. Setting

All participants were in hospital (inpatients).

4. Interventions

We identified studies using five interventions:

a. Zuclopenthixol acetate

The standard dose of zuclopenthixol acetate for adults is 50 mg to 150 mg intramuscular at intervals of two to three days. Some may need an additional injection one or two days after the first injection and the maximum cumulative dosage is 400 mg over a two-week period (Lundbeck 2011).

Bahrain 1996 used the doses of 50 mg to 200 mg intramuscular repeating every 24 to 48 hours (if clinically indicated). The initial mean dose was 106 mg for acute psychosis, 108 mg for mania and 115 mg for exacerbation of chronic psychosis. In Canada 1994, the initial dose of zuclopenthixol acetate was 50 mg to 150 mg every three days (mean dose of 117.6 mg per three days). The doses of 100 mg every two to three days were used by France 1988 while Malaysia 1998 used higher doses of 100 mg to 200 mg every six hours. Nordic 1993 used zuclopenthixol acetate 50 mg to 200 mg depending upon severity (not less than 24-hour interval between injections). Here, the average number of doses given during the study intervention period was two (range one to four). In South Africa 1997, people were treated with intramuscular zuclopenthixol acetate 150 mg on entry into the study and subsequently with oral zuclopenthixol 25 mg daily after 24 hours. A dose of 150 mg every three days was used by South Africa 1996. Thailand 2002 used 50 mg to 100 mg repeating every 12 hours as required. China 1997 used the lowest dose of zuclopenthixol acetate intramuscular (25-50 mg every three days), and compared this to zuclopenthixol acetate 50-100 mg (every three days).

b. Haloperidol, oral and intramuscular

Bahrain 1996 used a haloperidol intramuscular dose of 10 mg which was repeated on an 'as required' basis. All participants were subsequently on oral haloperidol throughout the study period. Mean intramuscular daily doses of haloperidol per patient were 25.6 mg for acute psychosis, 15.6 mg for mania and 11.25 mg for exacerbation of chronic psychosis. Initial dosage of liquid haloperidol 10 to 30 mg per day, divided in three doses was used in Canada 1994 (mean daily dose was 18.9 mg). Malaysia 1998 used haloperidol intramuscular dose of 10 mg every six hours as required. Nordic 1993 employed haloperidol intramuscular at a dose of 5-10 mg (maximum of four times/day), and switched to oral haloperidol when participants were co-operative. The average number of haloperidol injections used in this study varied between one and 11. The total haloperidol doses received (both intramuscular + oral) varied from one to 26. South Africa 1997 used a haloperidol intramuscular dose of 10 mg initially on entry into the trial arm and then oral haloperidol 10 mg after 24 hours. Thailand 2002 employed haloperidol intramuscular dose of 5-10 mg repeating every six hours as required.

c. Zuclopenthixol oral [also known as zuclopenthixol hydrochloride (zuclopenthixol dihydrochloride)] and conventional formulation of zuclopenthixol intramuscular

The usual starting dose of zuclopenthixol hydrochloride for adults is 10-50 mg/day, which may be increased by 10-20 mg every two to three days in acute psychosis. The usual therapeutic range is 20 mg to 60 mg daily. The usual maintenance dose is 20-40 mg/day and the daily dosage higher than 100 mg is not recommended (Lundbeck 2011).

One of the trial arms in Nordic 1993 used conventional formulation of zuclopenthixol, intramuscular dose of 10-20 mg (maximum of four times/day), switching to oral zuclopenthixol when people were co-operative. The number of intramuscular doses given varied widely between one to 12 during the study intervention period, and average daily doses of zuclopenthixol (both intramuscular + oral) given were generally 15–30 mg (oral doses were converted to equivalent intramuscular doses). The total number of zuclopenthixol doses received (both conventional zuclopenthixol intramuscular + oral zuclopenthixol) ranged from one to 22. South Africa 1997 used an initial dose of 150 mg/24 hours (zuclopenthixol acetate) followed by oral zuclopenthixol 25 mg/day.

d. Chlorpromazine, oral and intramuscular

Only one study, France 1988 used chlorpromazine intramuscular (dose of 100 to 300 mg), one to three times a day, switching to oral when people became co-operative.

e. Clothiapine, oral and intramuscular

Clothiapine is a low potency antipsychotic drug that is used in South Africa as a standard treatment in emergency psychiatry (Berk - personal communication). South Africa 1996 used an initial clothiapine intramuscular dose of 40 mg per injection, and a total daily dose of 80–160 mg was given in divided doses, either orally or intramuscular.

No studies compared zuclopenthixol acetate with an intervention that was considered as non-standard for the setting of the trial. Our search could not find any suitable studies for inclusion comparing zuclopenthixol acetate to other agents such as olanzapine, quetiapine, risperidone, aripiprazole, promethazine or midazolam.

5. Outcome measures

Apart from leaving the study early and use of additional medication, most outcomes, even those later made binary, were measured on the rating scales listed below.

Several trials presented findings in graphs or by P values alone. Graphical presentation made it impossible to acquire data for synthesis, as P values were commonly used as a measure of association between intervention and outcomes, instead of showing the strength of the association. Many did not provide standard deviations and previous requests for further information from authors remain unanswered. No new requests were made for 2003. For the 2011 update, a request was made to acquire data for Lamure 2003.

5.1 Mental state

5.1.1 Brief Psychiatric Rating Scale - BPRS

A brief rating scale used to assess the severity of a range of psychiatric symptoms, including psychotic symptoms. The scale has 16 items, and each item can be defined on a seven-point scale varying from 'not present' to 'extremely severe'. Scoring: high score is poor (Overall 1962).

5.2 Global state

5.2.1 Clinical Global Impression - CGI

A rating instrument commonly used in studies on schizophrenia that enables clinicians to quantify severity of illness and overall clinical improvement during therapy. A seven-point scoring system is usually used with low scores indicating decreased severity and/or greater recovery and higher (Guy 1976).

5.3 Behaviour

5.3.1 Nurses Observational Scale of Inpatients Evaluation - NOSIE

An 80-item scale with items rated on a five point scale from zero (not present) to four (always). Ratings are taken from behaviour over the previous three days. The seven headings are: social competence, social interest, personal neatness, co-operation, irritability, manifest psychosis and finally, psychotic depression. Scoring ranges from zero to 320 (Honingfeld 1965).

5.4 Adverse effects

5.4.1 Extrapyramidal Symptom Rating Scale (ESRS)

This consists of a questionnaire of parkinsonism symptoms which is a nine-item scale in addition to a physician's examination for parkinsonism and dyskinetic movements which includes eight items, and finally, a clinical global impression of tardive dyskinesia. High score is poor (Chouinard 1980). We used ESRS data in Canada 1994 to assess the adverse effects; dyskinesia, dystonia and parkinsonism.

5.4.2 UKU Side Effects Rating Scale (UKU-SERS)

This scale comprises four major topics: psychic side effects (10 items), neurological side effects (eight items), autonomic side effects (11 items) and other side effects (19 items). Each item is defined by means of a four-point scale where zero means not/doubtfully present. Scoring ranges from zero to 144 (Lingjaerde 1986). We used UKU-SERS data in Bahrain 1996, Malaysia 1998 and Nordic 1993 to assess adverse effects; dystonia , hyperkinesia, hypokinesia, restlessness(motor akathisia), rigidity, tremor, dizziness, dry mouth (decreased salivation) and blurred vision.

5.4.3 TESS Treatment Emergent Symptom Scale

This is an independently formatted six-item scale which is used to assess the presence and intensity of psychotropic medication side effects. It is used whenever it is necessary to record the presence of a symptom not printed on Dosage Record and Treatment Emergent Symptoms (DOTES) scale (Guy 1976).

6. Outcome scales unable to use

We found following outcome scales used by the included studies but their data were inadequate for the analysis.

6.1 Nurses Clinical Global Impression (NCGI)

No reference to this is given in the study that employs this measure (Canada 1994). The review authors suspect that this is the same as the CGI but rated specifically by nursing staff.

6.2 Bech-Rafaelsen Mania Ration Scale (BRMS/BRMAS)

A mania rating scale consisting of 11 items constructed for assessing the severity of the maniac state. Each item is defined on a five-point scale from zero (not present) to four (severe or extreme). Scoring ranges from zero to 44 (Bech 1979).

6.3 Simpson Angus Scale (SAS)

This is a 10-item rating scale that has been used widely for assessment of neuroleptic-induced parkinsonism (Simpson 1970).

7. Missing outcomes

None of the studies evaluated satisfaction with care and we have no direct economic data. We have made a request to obtain economic data from Lamure 2003.

8. Funders

Three studies, Bobon 1989 (excluded), France 1988 (included), and Nordic 1993 (included) showed striking similarities in their methodology and reporting of results. One paper, using a sub-sample from Bobon 1989, stated that the authors sent the data to Lundbeck for analysis. A Lundbeck employee was an author for Nordic 1993 and two Lundbeck employees were authors for France 1988. Lundbeck provided sponsorship for statistical analysis in South Africa 1997.

Excluded studies

Most excluded studies were not controlled trials or did not evaluate the acetate form of zuclopenthixol. The uncontrolled trials tended to be open clinical studies where outcomes in the same people were compared before and after using zuclopenthixol acetate. Of the controlled studies, most evaluated oral zuclopenthixol and not the acetate form.

Bobon 1989 met all eligibility criteria except one. This study involved acutely ill psychotic people and allocated them to zuclopenthixol acetate or haloperidol. Bobon 1989 stated that envelopes were employed and blocks of four designated. However, the number of patients in each treatment group within this study was very unbalanced (zuclopenthixol acetate - 55, haloperidol - 37). The paper suggested that probably not all hospitals in this study

had used the "four envelopes randomisation of each block" and we are therefore unable to use this study.

Awaiting assessment

One study (Lamure 2003), an economic evaluation, is awaiting assessment. Further data for its analysis have been requested.

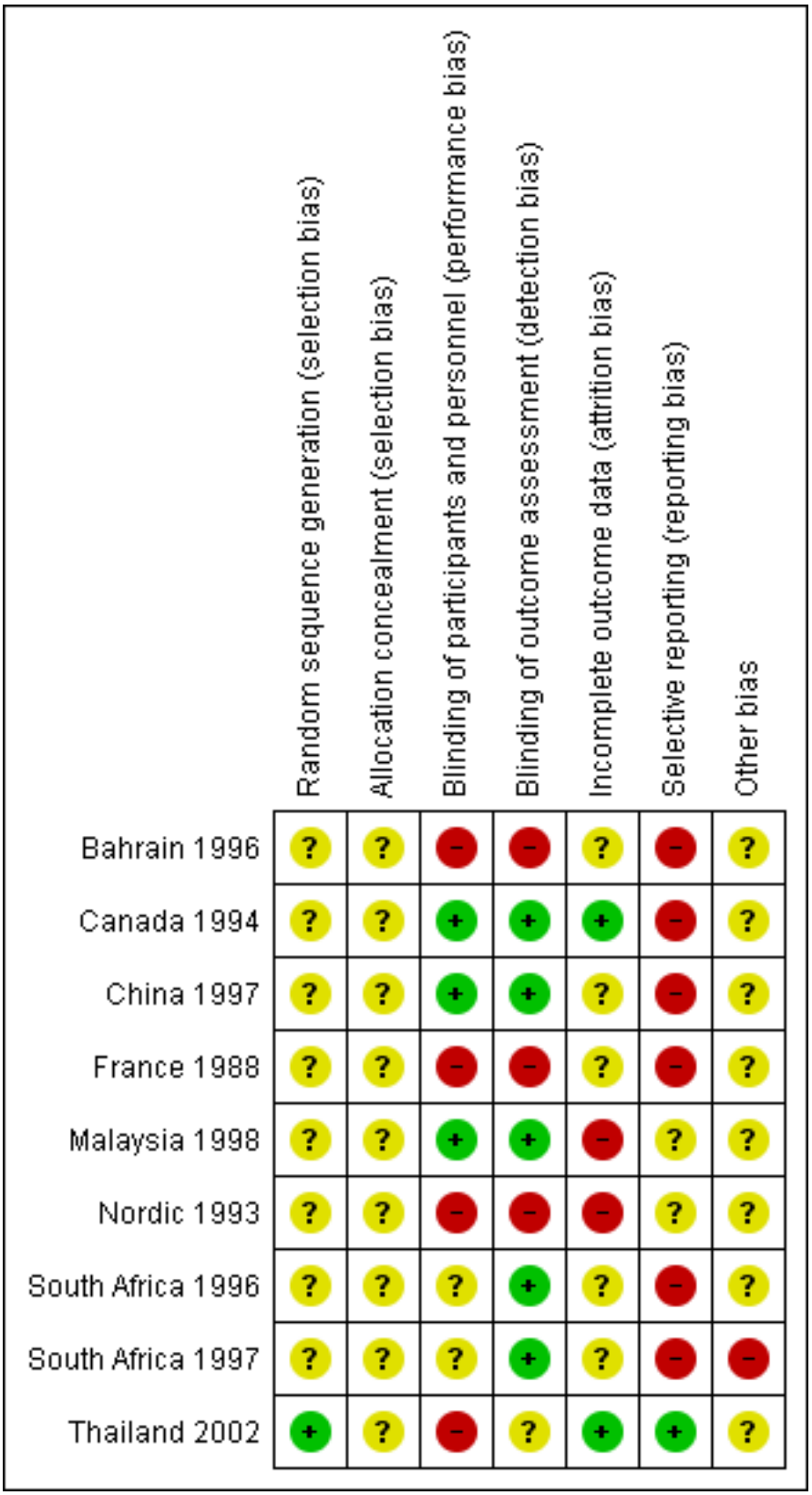
Ongoing studies

We know of no ongoing trials.

Risk of bias in included studies

Overall, the quality of reporting was poor with direct repercussions for the reliability of results (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Most of the included studies did not make explicit the process by which allocation to the intervention groups was undertaken. Thailand 2002 stated that an attending psychiatrist undertook allocation of people to treatment groups by drawing lots.

Blinding

Four studies stated that blind evaluation of outcome was undertaken (Canada 1994; Malaysia 1998; South Africa 1996; South Africa 1997). Blinding was present for some outcomes (some BPRS items) in Thailand 2002. The other studies stated that there was no blinding. In the blind or partially blind studies, this part of the methodology was not tested.

Incomplete outcome data

Canada 1994, South Africa 1997 and Thailand 2002 had no people leaving the study early and everyone was included in the analysis. Bahrain 1996 had one person leaving early because of the development of hypotension. Four studies actively excluded people from the analysis (France 1988; Nordic 1993; Malaysia 1998; South Africa 1996). South Africa 1996 excluded four out of 42 people because of 'protocol non-compliance'. France 1988 excluded two out of 118 people but the reasons were unclear. Nordic 1993 excluded 21 out of 169 because of 'protocol non-compliance' and suggested that this was because these people had received additional medication. No information, however, is available as to which group the people who withdrew had been originally allocated. A further eight people left Nordic 1993 early for unclear reasons and, again, it was not stipulated from which group they left. This study also had very unbalanced numbers in each arm. This was said to be due to the Steering Committee deciding to pool results of two trials originally designed to be independent. The study reports state that this decision was taken because the protocols were identical and the activities of both studies were co-ordinated by the same Steering Committee. Six people were withdrawn from Malaysia 1998, two because of a recent history of marijuana use.

Selective reporting

Many studies presented findings in graphs, in percentiles or by P values alone. P values were commonly used as a measure of association between intervention and outcomes instead of showing the strength of the association. Many did not provide standard deviations or did not give any information.

Other potential sources of bias

As the studies are generally not of high quality, it is possible that there are other biases apart from those mentioned above. Bahrain 1996 was an open-ended controlled trial while Nordic 1993 was an open controlled multicentre trial. Both could be prone to observer and other biases. A Lundbeck employee was an author for Nordic 1993. In Bahrain 1996, there was limited information with regard to statistical analysis, data collection and interview process. Canada 1994 was conducted under double-blind conditions (for participants and blind evaluation of outcome only). Dosages of each medication were adjusted by the research psychiatrist. France 1988 was not a double-blind study and two Lundbeck employees were authors. In Malaysia 1998, it was not clear whether all necessary confounding factors were accounted for at the baseline and also in the analysis. The number of aggressive episodes and the doses of lorazepam were not considered as outcome variables in South Africa 1997, and the sponsorship for its statistical analysis was provided by Lundbeck.

Effects of interventions

See: **Summary of findings for the main comparison** ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE for acute schizophrenia and similar serious mental illnesses; **Summary of findings 2** ZUCLOPENTHIXOL ACETATE (HIGH DOSE) compared to ZUCLOPENTHIXOL ACETATE (LOW DOSE) for acute schizophrenia and similar serious mental illnesses

1. COMPARISON: ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE

This comparison involves 522 people from eight studies.

1.1 Sedation

Studies evaluated sedation using different instruments. Reporting of this important outcome was limited. Canada 1994 (n = 40) found that although more people receiving zuclopenthixol acetate were sedated compared with those allocated haloperidol at two hours (risk ratio (RR) 0.60, 95% confidence interval (CI) 0.27 to 1.34), four hours (RR 0.74, 95% CI 0.54 to 1.00) and at eight hours (RR 0.72, 95% CI 0.51 to 1.03, Analysis 1.1), only the four-hour results are of borderline statistical significance (P = 0.05). France 1988 also reported more sedation among zuclopenthixol acetate users but presented no numbers. Bahrain 1996 also reported greater sedation with zuclopenthixol acetate compared with haloperidol but reported mean sedation scores with no variances. This renders these data unusable for analysis within this review. Nordic 1993 used a four-point scale from the UKU-SERS rating scale for sleepiness/sedation rated by nursing staff who knew what each of the patients had been given. These data were presented only in graphical form. It appeared to show that whilst zuclopenthixol acetate and dihydrochloride were similarly sedative, both appeared more sedative than haloperidol. However, neither statistical tests nor confidence intervals were provided. Finally, South Africa 1996 found no difference between clotiapine and zuclopenthixol acetate groups for sedation but no numerical data were given.

We had hoped to report outcomes of tranquillisation (primary outcome) but found no data.

1.2 Global state

Canada 1994 and the two newly added studies from Bahrain and Malaysia reported on the need for supplementary antipsychotics. Analysis of the pooled data yielded inconclusive results (n = 134, 3 RCTs, RR 1.49, 95% CI 0.97 to 2.30, I^2 = 79%). Additional use of benzodiazepines was, however, decreased for people allocated to zuclopenthixol acetate (n = 50, 1 RCT, RR 0.03, 95% CI 0.00 to 0.47, NNT 2, CI 2 to 4, Analysis 1.2). One small study (Thailand 2002) reported that people given zuclopenthixol acetate had fewer injections compared with those allocated to haloperidol IM (n = 70, RR requiring three or more injections over seven days 0.39, 95% CI 0.18 to 0.84, Analysis 1.3).

All studies employed the same measure of 'clinical global impression' (CGI). Bahrain 1996, Canada 1994 and Thailand 2002 all reported scores but only Canada 1994 included standard deviations. According to all studies, no significant difference was

found between zuclopenthixol acetate and other antipsychotics at the end of the follow-up period. Because of poor reporting of these data, however, only Canada 1994 could be analysed (n = 40, mean difference (MD) -0.05, 95% CI -0.75 to 0.65, Analysis 1.4).

1.3 Behaviour

We found no data on episodes of aggression or harm to self or others. Canadian researchers used a rating scale to assess behaviour (Nurses Observational Scale for Inpatient Evaluation). The total score showed a borderline level of statistical significance (P = 0.10) favouring haloperidol but the difference in the average score was about five points (zero to 320 points range, n = 40, MD -4.82, 95% CI -10.46 to 0.82, Analysis 1.5).

Nordic 1993 reported the mean and range of injections given (zuclopenthixol acetate - range one to four injections; 'standard' care - range one to 12). These data were not suitable for analysis in this review.

1.4 Mental state

For the outcome of 'no important improvement in mental state' pooled data from Nordic 1993 and Canada 1994 found no difference between people allocated to zuclopenthixol acetate and those given 'standard care' (n = 188, RR 0.86, 95% CI 0.39 to 1.86, Analysis 1.6).

France 1988, Nordic 1993 and South Africa 1996 all reported graphs of declines in Brief Psychiatric Rating Scale scores but it was impossible to extract any data. Bahrain 1996 and Thailand 2002 presented means and P values but no standard deviations. Canada 1994 did report slightly skewed continuous data, but again there was no significant difference between groups. Although few data could be used, however, all studies reported no significant difference between zuclopenthixol acetate and other antipsychotics at the end of the follow-up period.

1.5 Adverse effects

Nordic 1993 (n = 148) reported no significant difference in adverse effects for people receiving zuclopenthixol acetate compared with those allocated haloperidol at one day (RR 0.54, 95% CI 0.25 to 1.19), three days (RR 0.97, 95% CI 0.56 to 1.68) or six days (RR 0.74, 95% CI 0.43 to 1.27, Analysis 1.8). France 1988 also reported the outcome of adverse effects in general and at the third day of treatment, zuclopenthixol acetate users had fewer adverse effects than those in the chlorpromazine group. However, no numerical data were reported.

Compared with haloperidol (Bahrain 1996; Canada 1994; Bahrain 1996; Nordic 1993) and clotiapine (South Africa 1997), people allocated zuclopenthixol did not seem to be at any more risk of a range of movement disorders. The addition of South Africa 1997 to the outcome of 'use of antiparkinson medication' (n = 276, 4 RCTs, RR 0.96, 95% CI 0.80 to 1.15, Analysis 1.9) adds heterogeneity (I^2 = 54%). This is because clotiapine does cause significantly less parkinsonism than the other haloperidol comparison groups.

Canada 1994 reports skewed continuous data for measures of parkinsonism (a total score and severity score), postural disorder, and non-postural (dyskinetic) movements (a total score and severity score). The raw data are equivocal, finding no difference between the zuclopenthixol acetate and haloperidol (Analysis 1.10).

Studies reported a series of other adverse effects over different time periods (Analysis 1.11). Not one, however, suggested that zuclopenthixol acetate was any worse than haloperidol or clotiapine. Three studies found no difference in the proportion of people getting blurred vision/dry mouth between 24 hours (n = 192, 2 RCTs, RR 0.90, 95% CI 0.48 to 1.70) and six days (n = 38, 1 RCT, RR 2.02, 95% CI 0.45 to 9.16). Similarly, dizziness was not more frequent for those allocated zuclopenthixol acetate compared with haloperidol (n = 192, 2 RCTs, RR at 24 hours 1.15, 95% CI 0.46 to 2.88). South Africa 1996 reported no differences for palpitations (RR 1.62, 95% CI 0.34 to 7.80) and Thailand 2002 found no difference for developing a reaction at the injection site (RR 0.11, 95% CI 0.00 to 5.74).

1.6 Leaving the study early

All eight studies were included in the analysis for leaving the study early. It is not clear from some trials whether people were indeed free to leave but there was no difference between treatments for this outcome (n = 522, RR 0.85, 95% CI 0.31 to 2.31, Analysis 1.12).

1.7 Missing outcomes

None of the studies reported tranquillisation (our primary outcome), sudden or unexpected death, hospital and service outcomes, satisfaction with care or economic outcomes.

1.8 Publication bias

There were too few studies to enter into a meaningful funnel graph for assessing presence of possible small study or publication bias.

1.9 Subgroup and sensitivity analysis

Where data permitted, sensitivity analyses were undertaken in order to see if sub-grouping data resulted in important changes in the results. Seven such sub-groupings were pre-specified as described above, although we had recognised that data were likely to be too sparse to undertake all of them.

1.9.1 Rigorous versus less rigorous criteria for diagnosing schizophrenia

Only South Africa 1997 did not employ operational criteria for the diagnosis of schizophrenia. This small study (n = 44) only reported usable data on leaving the study early. This was not one of our pre-designated primary outcomes and so sensitivity analysis was not undertaken.

1.9.2 Published versus unpublished trials

The only unpublished study was France 1988 which had no useable data on any of the pre-specified primary outcomes. Sensitivity analysis was therefore not possible.

1.9.3 High quality studies versus others

No study was of exceptional quality (Figure 2). We did judge the Malaysia 1998 study to be somewhat better than the others. The only effect of removing the Malaysian study from the data pool was that the heterogeneous analyses for requiring additional medication became homogeneous and pooled results significantly favoured zuclopenthixol acetate (n = 90, 2 RCTs, RR additional neuroleptics 2.19, 95% CI 1.35 to 3.54).

1.9.4 Acute versus non-acute symptoms

All participants presented with acute symptoms. Sensitivity analysis using this variable was therefore impossible.

1.9.5 Oral versus intramuscular antipsychotic

Zuclopenthixol acetate is always given intramuscularly. No study employed exclusively oral or exclusively intramuscular routes for administering standard drug care to people in the comparison groups. Sensitivity analysis using this variable was, therefore, not possible.

1.9.6 Violent versus non-violent behaviour

Although all the studies reported treating people who were acutely ill, only South Africa 1996 and Thailand 2002 explicitly stated that the participants were also aggressive. Because information on the violence or non-violence of participants is unavailable for the majority of studies, sensitivity analysis using this variable was not done.

1.9.7 Reduced dosage versus standard dosage zuclopenthixol

Bahrain 1996, Canada 1994 and Thailand 2002 included reduced doses (less than 100 mg) of zuclopenthixol acetate in their interventions. However, none of these studies distinguished between the patients receiving low doses and those receiving standard doses when reporting on the outcomes of interest. Sensitivity analysis using this variable was therefore also impossible.

1.10 Heterogeneity

Few data were pooled in this review. For the outcome of needing additional antipsychotic drugs, pooled data are heterogeneous (I^2 = 79%). This seems largely as a result of Malaysia 1998. Removing this study reduces I^2 to 54% and changes the result to one that is statistically significantly in favour of haloperidol (n = 90, 2 RCTs, RR 2.19, 95% CI 1.35 to 3.54). It is unclear from the design of the study why this may be so and we continue to present pooled data. It is feasible that random error or, especially with such small studies, systematic bias is contributing to these results. We could easily have failed to identify several other trials that, when pooled, would have given a more homogeneous result.

The only other result containing heterogeneity is the study for the risk of needing antiparkinsonism medication. In this case the cause of heterogeneity is clear. One study out of the four (South Africa 1996), uses clotiapine instead of haloperidol as a comparison drug. Clotiapine causes few movement disorders compared with haloperidol, and removal of this single study restores homogeneity but does not materially affect the result.

2. COMPARISON: ZUCLOPENTHIXOL ACETATE HIGH DOSE versus ZUCLOPENTHIXOL ACETATE LOW DOSE

This comparison involves 30 people from one study (China 1997) in which the trial author defined 25-50 mg as low dose and 50-100 mg as high dose. Nordic 1993 compared zuclopenthixol acetate 50-200 mg intramuscular dose (not less than 24-hour interval between injections) with zuclopenthixol acetate 10-20 mg intramuscular dose (maximum of four times/day), but its data were limited for the analysis.

2.1 Mental state

China 1997 evaluated mental state using BPRS. This study did not find any significant difference for the outcomes of 'not recovered' (n = 30, RR 1.10, 95% CI 0.69 to 1.76, Analysis 2.1), 'not markedly improved' (n = 30, RR 1.00, 95% CI 0.51 to 1.95, Analysis 2.2) and 'not improved' (n = 30, RR 0.60, 95% CI 0.17 to 2.07, Analysis 2.3) between high dose and low dose zuclopenthixol acetate.

2.2 Adverse effects

China 1997 evaluated adverse effects using Treatment Emergent Symptom Scale (TESS). Again, this study did not find any significant difference in adverse effects between high dose and low dose of zuclopenthixol acetate (n = 30, RR 2.33, 95% CI 0.74 to 7.35, Analysis 2.4).

DISCUSSION

Zuclopenthixol acetate has been widely proposed as a product specifically designed for the management of people with acute psychotic manifestations during psychiatric emergencies. Low frequency of side effects and good tolerability has also been stressed by open clinical studies and material produced for marketing purposes. The search for controlled clinical trials, however, found a small number of studies, some presenting important methodological flaws.

Summary of main results

1. COMPARISON: ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE

Overall, the quality of data was not good (Summary of findings for the main comparison).

1.1 Missing data

Among the seven groups of pre-defined outcomes in our protocol for this review, only four were addressed by the studies. For example, we had hoped to report outcomes of tranquillisation (primary outcome) but found no data. This seems remarkable considering the wide use of zuclopenthixol acetate. We also failed to find data on hospital and services outcomes, satisfaction with care or economic outcomes. There was no information on outcomes that are clinically important such as violent incidents, disturbed behaviour, compulsory treatment and hospitalisation. There is a need for wide consensus on outcomes that are meaningful for trials in this area.

1.2 Sedation

Although tranquillisation was the primary outcome, we took sedation as a 'second best' but even those studies that reported it used different instruments and reporting was very poor. One small study did report usable data (Canada 1994, n = 40) and found no clear difference between zuclopenthixol acetate and haloperidol at two, four and eight hours. Less than half the group was sedated by two hours; nearly three-quarters by four. Two hours, however, is a long time to wait for sedation if an episode remains dangerous so best - limited - data suggests that zuclopenthixol acetate may not be the best choice for acute tranquillisation or sedation.

1.3 Global state

Although data are very poor and are all from small studies, most point to some advantage in terms of global state for zuclopenthixol acetate. This could be a function of it being longer acting than haloperidol. Analysis of pooled data did not suggest that zuclopenthixol acetate helped global state more than haloperidol for the proxy measure of 'needing additional antipsychotics' but additional use of benzodiazepines was decreased for people allocated to zuclopenthixol acetate (Analysis 1.2). Another small study (n = 70) reported that people given zuclopenthixol acetate had fewer injections compared with those allocated to haloperidol IM (Analysis 1.3) and this is most important when each administration of injection is likely to be coercive.

1.4 Mental state and behaviour

For 'no important improvement in mental state' zuclopenthixol acetate was not clearly different to intramuscular haloperidol (Analysis 1.6) - about 90% in both groups had improved by 36 hours. It may, however, have needed several injections of the control drug to have this effect. We found no data on episodes of aggression or harm to self or others and scale ratings from the Canada 1994 were impossible to interpret.

1.5 Adverse effects

The larger Nordic 1993 (n = 148) reported no significant difference in adverse effects for people receiving zuclopenthixol acetate compared with those allocated haloperidol at one, three or six days. Around 70% to 80% of people did not report an adverse effect in either group. This does not seem entirely likely and may reflect either trial design or the coercive relationship that could have been part of care within the study. Movement disorders were equally prevalent for both groups (< 20%) when the comparison was haloperidol. Clotiapine does seem to cause considerably less movement disorders than zuclopenthixol acetate and other classical antipsychotics (Carpenter 2001).

Studies reported a series of other adverse effects over different time periods. Overall, reported adverse event rates were low (< 10% to 15%) and not one suggested that zuclopenthixol acetate was any worse than haloperidol or clotiapine. There was no difference between treatments for 'leaving the study early' (Analysis 1.12). It was not clear from some trials whether people were indeed free to leave so we do not think this outcome is of much value in the context of these trials.

we do not think this outcome is of much value in the context of these trials.

2. COMPARISON: ZUCLOPENTHIXOL ACETATE HIGH DOSE versus ZUCLOPENTHIXOL ACETATE LOW DOSE

Data from this new comparison came from one small study of limited quality (Summary of findings 2).

2.1 Mental state

China 1997 did not find any significant difference in BPRS outcomes of 'not recovered', 'not markedly improved' and 'not improved' between high dose (50-100 mg/injection) and low dose (25-50 mg/injection) zuclopenthixol acetate. This trial included only 30 people in total so these findings can only be considered as preliminary but do suggest that the lower doses (as low as 25 mg) may be just as effective as up to 100 mg injections.

2.2 Adverse effects

China 1997 did not find any significant difference in adverse effects between high dose (50-100 mg/injection) and low dose zuclopenthixol acetate (25-50 mg/injection) when measured using TESS. Again, this single study is of limited power and should be replicated.

3. Publication bias and sensitivity analysis

Because of the surprisingly few studies, all of which were small, measures of publication bias and sensitivity analyses were meaningless.

Overall completeness and applicability of evidence

1. Completeness

Our results and conclusions depend upon limited number of studies and these all had their its own methodological limitations (trial limitations - Figure 2, outcome limitations - Summary of findings for the main comparison; Summary of findings 2). Nevertheless, we believe we have included most of the existing evidence.

Certainly, studying treatment effects of zuclopenthixol acetate during an acute phase of illness brings unique difficulties. However, the outcomes covered in these important trials do seem most limited and, without much or any additional effort more data could have been reported that would have been of great interest. It is not difficult to report 'tranquil' or 'time to discharge' or 'violent incident'. All the more reason for global agreement of a minimal data set to be reported in such trials (see Implications for research).

2. Applicability

Although schizophrenia trials are often conducted on very different people than are seen in routine practice and evaluate treatments that are rigid, the studies in this review, undertaken in situations of acute emergency, may be somewhat more applicable than average.

Quality of the evidence

Overall the quality was poor (Summary of findings for the main comparison; Summary of findings 2), therefore, any conclusions must be undertaken with caution. Much of this poor quality reporting is easily avoidable. For example, only one study made the means of randomisation explicit, studies stressed the importance of blinding but did not test it and three out of eight studies excluded people from the analysis after randomisation and none of the three described from which group patients were excluded. Outcomes were commonly reported using graphs and P values instead of tables and confidence intervals. There was an emphasis on the use of continuous data, which are less useful than binary (yes/no) outcomes in providing more direct interpretation. The excessive use of graphs did not allow the review authors to find numbers needed to calculate many measures of effect.

Potential biases in the review process

The search for this review and the updates largely depends on the Cochrane Schizophrenia Group's register of trials. Every effort is made to ensure that this is comprehensive, but it is not a good

source of unpublished data. It is possible that we have failed to identify other small unpublished or very inaccessible studies. In a review just compiled of small studies even a few other trials may make considerable difference.

Throughout the review process we have applied strict criteria to identify included studies and their methodological flaws. It is possible that published articles would not have reported all the information due to word limitations in journals. We used 'unclear risk' in the 'Risk of bias' tables to indicate when there was no further information. We also had to translate studies (e.g. China 1997) and aimed to minimise translation errors but some could remain.

Agreements and disagreements with other studies or reviews

At the time of this 2011 update, we could not identify any other reviews other than different versions of this same review (Coutinho 2000a; Fenton 1997; Fenton 2000; Fenton 2001; Gibson 2004)

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with serious mental illness and their carers

There is no evidence to support claims made in open clinical trials that zuclopenthixol acetate has fewer side effects than standard treatment. It may be administered less frequently but its effects probably last considerably longer than drugs such as haloperidol. There is some new evidence that lower doses (as low as 25 mg) may be just as effective as the higher doses (up to 100 mg).

2. For clinicians

Recommendations on the use of zuclopenthixol acetate in preference to 'standard' and 'non-standard' treatments for the management of psychiatric emergencies have to be viewed with caution. This review did not find any suggestion that zuclopenthixol acetate is *more effective* than 'standard' care in controlling aggressive/disorganised behaviour, acute psychotic symptoms, or preventing adverse effects. The enthusiasm of open clinical studies regarding the 'effectiveness' of zuclopenthixol acetate for those with acute psychotic disturbance is in contrast with the paucity of evidence from the very few randomised controlled trials. Moreover, the study with the largest sample size (Nordic 1993) has important methodological flaws. There were no data relating directly to tranquillisation, but four studies suggested that patients using zuclopenthixol acetate had more intense and earlier sedation. Nevertheless, even this result is open to question as reporting of the data was so poor. The new study included in this review (China 1997) did suggest that lower doses of zuclopenthixol acetate may be adequate.

3. For policy makers or funders of research

This is a difficult area for policy makers, but zuclopenthixol acetate does have some evidence to support its use - but not enough. Evidence is very far from 'good' but does point to zuclopenthixol acetate being helpful for managing acutely disturbed people. In comparison to other drugs it is not clearly worse than others.

The whole area of pharmacological management of acutely disturbed people is under-researched. Funders in regions using zuclopenthixol acetate should consider supporting a definitive study in comparison to another accessible drug used for the same purposes.

Implications for research

1. General

This review highlighted the efficacy and necessity of quality controlled clinical trials and how further studies are required to address the claims made by several open clinical studies. Reporting was very poor even in those trials published after the CONSORT statement of 1996 (Begg 1996; Moher 2001). There now is no excuse for poor reporting of studies which is both wasteful and unethical.

2. Specific

2.1 Methods

The psychiatric emergency situation is a difficult research environment. Nevertheless, adherence to a good quality pragmatic trial protocol will avoid many methodological problems seen in the studies in this review. Allocation concealment is a fundamental part of trial methodology. If readers are to be reassured that selection bias was minimised, the randomisation process should be clearly described. Double-blind evaluation of the outcomes is an important strategy for avoiding performance and detection bias. For many outcomes of interest in this review blinding would seem important and should always be attempted and, preferably, tested. If blinding cannot be used then outcomes that are less prone to observer bias should be preferred.

Trialists should avoid withdrawing people from analysis after randomisation, perform an intention-to-treat analysis and describe from which groups withdrawals came.

2.2 Setting

As some suggestion exists that zuclopenthixol acetate could be used in the community (Abdullahi 1993), future studies of zuclopenthixol acetate could take into account its use in the community as well as in hospital.

2.3 Outcomes

Tranquillisation may be a more useful outcome than sedation. Studies should also consider hospital and services outcomes, satisfaction with care, and economic measures. Concrete outcomes of disturbance such as 'disturbed episode', 'use of detention order', 'use of special nursing observation' or, for those in the community, 'avoiding hospitalisation' would also be of interest. Agreeing on a universally applicable minimum data set could be of great value in this area and it is encouraging to see that, since the first version of this review much progress has been made in devising systems for this to happen in other areas of health care (COMET). It is, we hope, only a matter of time before this approach is taken in relation to people who are in need of acute tranquillisation.

2.4 Reporting

Authors should present measures of association between intervention and outcome, for example, relative risks, odds-ratios, risk or means difference, and the raw numbers. Binary outcomes should be reported as well as, or in preference to, continuous results as they are easier to interpret. It is strongly suggested that authors report confidence intervals and statistical power for

comparisons presented in the papers. If P values are used, the exact value should be reported.

We have also made suggestions for the design of a new trial relevant to zuclopenthixol acetate (Table 2).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bahrain 1996

Methods	Allocation: randomised, no further information. Blinding: not blinded at outcome. Design: parallel. Duration: 6 days. Consent: mentioned.
Participants	Diagnoses: schizophrenic psychosis, affective psychosis, paranoid states (ICD 9). History: acutely ill or exacerbation of chronic illness. N = 50. Age: accepted 18-65. Sex: both. Setting: hospital.
Interventions	1. Zuclopenthixol acetate IM: dose 50-200 mg every 24-48 hours, no oral antipsychotic. N = 26. 2. Haloperidol IM: dose 10 mg repeated as required, switched to oral when co-operative. N = 24. Anti-parkinsonian drugs and benzodiazepines allowed.
Outcomes	Global state: needing additional injections of allocated drug, needing additional injections of benzodiazepines. Leaving the study early. Adverse effects: CGI, UKU-SERS, use of antiparkinsonian drugs. Unable to use Global state: CGI, sedation scores, speed of remission (means, no SD). Mental state: BPRS, BRMS (means, no SD).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Bahrain 1996 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Patients were randomly allocated, no further information.
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One patient left the study, not accounted for in analysis.
Selective reporting (reporting bias)	High risk	Details of the statistical analysis method was not specified.
Other bias	Unclear risk	Diazepam was used if necessary and benztropine was used to treat side effects. Not clear whether these were accounted for analysis. Also, no further information on data collection and interview process.

Canada 1994

Methods	Allocation: randomised, stratified by sex, no further information. Blinding: double, placebos used. Design: parallel. Duration: 9 days. Consent: mentioned.
Participants	Diagnosis: schizophrenia (DSM III). History: acutely ill. N = 40. Age: accepted 18-65. Sex: both. Setting: hospital.
Interventions	1. Zuclopenthixol acetate IM: dose 50-150 mg every 3 days + placebo oral. N = 20. 2. Haloperidol orally: dose 10-30 mg/day + placebo IM. N = 20. Anti-parkinsonian drugs, additional zuclopenthixol acetate (50 mg) and additional haloperidol (10 mg) allowed.
Outcomes	Mental state: BPRS. Global state: CGI. Behavior: NOSIE. Sedation: number not sedated. Adverse effects: ESRS, prolactin levels. Unable to use Mental state: clinical interview (no data given). Behaviour: NCGI (no data given).

Canada 1994 *(Continued)*

	Adverse effects: blood pressure, pulse rate, ECG, blood tests, physical examination (no results given).
Notes	Blood tests included prolactin.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was done separately for men and women but no further information regarding sequence generation.
Allocation concealment (selection bias)	Unclear risk	No further information.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded at outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition.
Selective reporting (reporting bias)	High risk	For Nurses Clinical Global Impression (NCGI), only P value was given.
Other bias	Unclear risk	Double-blind conditions only.

China 1997

Methods	Allocation: not stated. Blinding: double blind. Design: parallel. Duration: 6 days. Consent: not clear.
Participants	Diagnoses: Schizophrenia. History: acute or chronic schizophrenia with acute onset episodes. N = 30. Age: accepted 18-65. Sex: both. Setting: hospital.
Interventions	Zuclopenthixol acetate (high dose) IM: dose 50-100 mg every 3 days. N = 15. Zuclopenthixol acetate (low dose) IM: dose 25-50 mg every 3 days. N = 15.
Outcomes	Mental state: BPRS. Adverse effects: TESS. Unable to use

China 1997 *(Continued)*

	Global state: CGI (No SD).
Notes	Length of illness: high dose group - 51.7 months on average. low dose group - 52.37 months on average.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Although the study is double blind, allocation is not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No further information.
Selective reporting (reporting bias)	High risk	No SD and mean values for BPRS and CGI outcomes.
Other bias	Unclear risk	No further information on data collection process.

France 1988

Methods	Allocation: randomised, no further information. Blinding: not double-blind. Design: parallel. Duration: 6 days. Consent: not mentioned.
Participants	Diagnoses: psychosis, mania (ICD 9). History: acutely ill or exacerbation of chronic illness. N = 118. Age: no information. Sex: both. Setting: hospital.
Interventions	1. Zuclopenthixol acetate IM: dose 100 mg every 2-3 days. N = 58. 2. Chlorpromazine IM: dose 100-300 mg 1-3 times/day, switched to oral when co-operative. N = 58.
Outcomes	Leaving the study early. Unable to use Mental State: BPRS, BRMS, CGI staff (no usable data). Sedation (no data given).

France 1988 *(Continued)*

	Adverse effects: UKU-SERS, blood tests (no results given).
Notes	1. Two people excluded from analysis - reason unknown. 2. Two authors working at Lundbeck. 3. Awaiting authors or Lundbeck's reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No further information regarding randomisation process.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Two patients were not taken in to analysis.
Selective reporting (reporting bias)	High risk	No data with regard to some adverse events.
Other bias	Unclear risk	Potential for other bias due to non-blinding.

Malaysia 1998

Methods	Allocation: randomised, no further information. Blinding: double. Design: parallel. Duration: 3 days. Consent: mentioned.
Participants	Diagnoses: exacerbated chronic schizophrenia, schizophreniform disorder (DSM-III). History: acutely disturbed (agitated or restless). N = 50. Age: accepted 18-65. Sex: both. Setting: hospital.
Interventions	1. Zuclopenthixol acetate IM: dose 100-200 mg every 6 hours as required. N = 23. 2. Haloperidol IM: dose 10 mg every 6 hours as required. N = 21. Anti-parkinsonian drugs and benzodiazepines allowed.
Outcomes	Global state: requiring additional injections of allocated drug. Adverse effects: UKU-SERS, leaving the study early.

Malaysia 1998 *(Continued)*

	Unable to use Mental state: BPRS, CGI (means, no SD).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No further information regarding randomisation process.
Allocation concealment (selection bias)	Unclear risk	The randomisation code was kept by the first author and was not revealed to others to maintain blindness. No further details with regard to allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Total of 50 patients entered the study, only 44 patients completed the study and were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	Baseline comparison table shows age, sex and ethnicity only.
Other bias	Unclear risk	Two different dosages for initial 10 participants and it is not clear whether this was accounted for analysis.

Nordic 1993

Methods	Allocation: randomised, no further information. Blinding: not double-blind. Design: parallel. Duration: 6 days. Consent: mentioned.
Participants	Diagnoses: psychosis, mania (ICD 9). History: acutely ill or exacerbation of chronic illness. N = 169. Age: accepted 18-65. Sex: both. Setting: hospital.
Interventions	1. Zuclopenthixol acetate IM: dose 50-200 mg (not less then 24 hr interval between injections). N = 83. 2. Haloperidol IM: dose 5-10 mg (maximum of 4 times/day), switched to oral when co-operative.N = 25. 3. Zuclopenthixol IM: dose 10-20 mg (maximum of 4 times/day), switched to oral when co-operative. N = 40. Anti-parkinsonian drugs and benzodiazepines allowed.

Nordic 1993 *(Continued)*

Outcomes	Adverse effects: UKU-SERS, use of antiparkinsonian drugs. Unable to use Mental State: BPRS, CGI, BRMS (results presented graphically, no SD). Sedation (results presented graphically, no SD). Blood tests (data not reported).
Notes	1. Twenty-one people excluded from analysis because of "protocol violation" after randomisation - no information regarding numbers per group. 2. One author working at Lundbeck. 3. Awaiting for authors' or Lundbeck's reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified randomisation but no information regarding random sequence generation.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	169 patients entered the study, statistical analysis comprised of only 148 patients.
Selective reporting (reporting bias)	Unclear risk	Some data were presented graphically, no SD.
Other bias	Unclear risk	Open controlled multicentre trial.

South Africa 1996

Methods	Allocation: randomised, no further information. Blinding: double-blind stated, but no oral placebo in intervention group 1. Design: parallel. Duration: 6 days. Consent: mentioned.
Participants	Diagnoses: psychosis, mania (ICD 9). History: acutely ill or exacerbation of chronic illness. N = 42. Age: accepted 18-65. Sex: male. Setting: hospital.
Interventions	1. Zuclopenthixol acetate IM: dose 150 mg every 3 days. N = 21.

South Africa 1996 *(Continued)*

	2. Clothiapine IM or oral: dose 80-160 mg/day. N = 17. Anti-parkinsonian drugs, lithium and benzodiazepines allowed.
Outcomes	Adverse effects: dry mouth/blurred vision by 6 days, use of antiparkinsonian medication, palpitations. Leaving the study early. Unable to use Mental status: BPRS, CGI, BRMS (mean scores reported graphically, no SD). Sedation (data not reported). Adverse effects: UKU, SERS (data not reported).
Notes	1. Four people excluded from analysis because of "protocol violation" after randomisation - no information regarding numbers per group. 2. Awaiting authors reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No oral placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	42 patients entered the study, 4 patients were excluded from the statistical analysis due to protocol violations.
Selective reporting (reporting bias)	High risk	Some adverse effects data were not reported.
Other bias	Unclear risk	Not clear whether necessary confounding factors were accounted for analysis.

South Africa 1997

Methods	Allocation randomised, no further information. Blinding: double-blind: stated but no oral placebo in intervention group 1. Design: parallel. Duration: 28 days. Consent: mentioned.
Participants	Diagnoses: schizophrenia N = 11, schizophreniform disorder N = 5, substance induced psychotic disorder N = 27, bipolar affective disorder N = 1. History: acutely ill or exacerbation of chronic illness. N = 44. Age: accepted 18-65.

South Africa 1997 *(Continued)*

	Sex: both. Setting: hospital.
Interventions	1. Zuclopenthixol acetate IM: initial dose 150 mg, then oral zuclopenthixol 25 mg/day. N = 10. 2. Haloperidol IM: dose 10 mg, then oral haloperidol: dose 10 mg/day. N = 6. Anti-parkinsonian drugs and benzodiazepines allowed.
Outcomes	Leaving the study early. Unable to use Mental state: BPRS, SAS (data pooled for all groups, not extractable for participants of interest). Global state: CGI (data pooled for all groups, not extractable for participants of interest). Sedation (results not reported). Adverse effects (results not reported).
Notes	Only those with schizophrenia or schizophreniform disorder were included in the review. Only data relating to 'leaving the study early' were possible to extract for schizophrenia and schizophreniform disorders.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No further information regarding the randomisation process.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No oral placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No further information.
Selective reporting (reporting bias)	High risk	Sedation and adverse effect results were not reported.
Other bias	High risk	Number of aggressive episodes and the doses of lorazepam were not outcome variables.

Thailand 2002

Methods	Allocation: randomised, no further information. Blinding: present for some outcomes. Design: parallel. Duration: 7 days. Consent: not mentioned.

Thailand 2002 *(Continued)*

Participants	Diagnoses: acute psychosis, schizophrenia with acute exacerbation, mania, other forms of psychosis (ICD 10). History: disturbed and aggressive behaviour, unresponsive to verbal intervention. N = 70. Age: accepted 18-65. Sex: both. Setting: hospital.
Interventions	1. Zuclopenthixol acetate IM: dose 50-100 mg repeated every 12 hours as required. N = 38. 2. Haloperidol IM: dose 5-10 mg repeated every 6 hours as required. N = 32. Oral antipsychotics and mood stabilisers allowed.
Outcomes	Global state: requiring additional injections of allocated drug. Adverse effects: presence of tremor, reaction at injection site. Unable to use Mental state: BPRS (means, inadequate data on SD). Global state: CGI (means, no SD).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Attending psychiatrist undertook allocation of people to treatment groups by drawing lots.
Allocation concealment (selection bias)	Unclear risk	No further information.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding was present for some BPRS outcomes, not for CGI outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition.
Selective reporting (reporting bias)	Low risk	P values and CI were reported for all outcomes and side effects were reported separately.
Other bias	Unclear risk	Some patients received other oral antipsychotics and mood stabilizers. It is not clear whether these unmeasured confounders were accounted for analysis.

(*) Studies with methodological problems.
Mental state scales
BPRS - Brief Psychiatric Rating Scale
CGI - Clinical Global Impression
BRMS - Bech-Rafaelsen Mania Ration Scale
SAS - Simpson Angus Scale

Behaviour
NOSIE - Nurses Observational Scale of Inpatients Evaluation
NCGI - Nurses Clinical Global Impression
Adverse effects
ESRS - Extrapyramidal Symptom Rating Scale
UKU-SERS - UKU Side Effects Rating Scale
TESS - Treatment Emergent Symptom Scale
CI - confidence interval; IM - intramuscular; SD - standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Amisden 1986	Allocation: not randomised, open clinical trial.
Amisden 1987	Allocation: not randomised, open clinical trial.
Anton 1962	Allocation: not randomised, case series.
Arango 2002	Allocation: randomised. Participants: people with schizophrenia and a history of violence. Interventions: zuclopenthixol decanoate, oral zuclopenthixol, not zuclopenthixol acetate.
Balant 1989	Allocation: not randomised, open clinical trial.
Balasubramanian 1991	Allocation: randomised. Participants: people with acute functional psychosis. Interventions: oral zuclopenthixol, oral chlorpromazine, not zuclopenthixol acetate.
Ban 1975	Three component studies. Study 1 phase 1: Allocation: not randomised, open clinical trial. Study 1 phase 2: Allocation: randomised. Participants: people with schizophrenia. Interventions: thioxanthene, chlorpromazine, placebo, not zuclopenthixol acetate. Study 2: Allocation: randomised. Participants: people with schizophrenia. Interventions: thiothixene, chlorprothixene, thioproperazine. not zuclopenthixol acetate. Study 3: Allocation: randomised. Particpants: people with schizophrenia. Interventions: oral thiothixene, oral chlorprothixene and oral clopenthixol, not zuclopenthixol acetate.
Bobon 1989	Allocation: randomised, but unequal numbers in groups said to be because hospitals probably "did not use the 4 envelopes randomisation of each block" Category C. Participants: acute psychoses. Interventions: zuclopenthixol acetate versus haloperidol IM and oral.
Burke 2002	Allocation: not randomised.
Chakravarti 1990	Allocation: not randomised, open clinical trial.
Conca 2003	Allocation: not randomised.

Study	Reason for exclusion
	Participants: people with catatonia including schizophrenia, psychosis and schizoaffective disorder. Interventions: zuclopenthixol acetate.
Dehnel 1968	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral clopenthixol, oral perphenazine, not zuclopenthixol acetate.
Fischer-Cornelssen	Allocation: not clearly stated. Participants: people with moderate and severe schizophrenia. Interventions: oral clozapine, oral chlorpromazine, oral haloperidol, oral trifluperazine and oral clopenthixol, not zuclopenthixol acetate.
Glenthoj 2000	Allocation: randomised. Participants: people with drug-naive, first-episode schizophrenia. Interventions: risperidone, oral zuclopenthixol, not zuclopenthixol acetate.
Gravem 1978	Allocation: not clearly stated. Participants: people with "mainly schizophrenia". Interventions: oral clopenthixol, oral cis (Z) -clopenthixol, not zuclopenthixol acetate.
Gravem 1981a	Allocation: not stated. Participants: people with classical or paranoid schizophrenia. Interventions: oral clopenthixol, oral cis (Z) -clopenthixol, not zuclopenthixol acetate.
Gravem 1981b	Allocation: not randomised, review article.
Gravem 1990	Allocation: randomised. Participants: people with schizophrenia, manic-depressive illness, paranoid psychosis. Interventions: single combined injection of zuclopenthixol acetate and zuclopenthixol decanoate, separate injections of zuclopenthixol acetate and zuclopenthixol decanoate. No comparison of zuclopenthixol acetate with standard treatment.
Heikkila 1981a	Allocation: not clearly stated. Participants: people with oligophrenia, schizophrenia. Interventions: oral clopenthixol, oral cis (Z) -clopenthixol, not zuclopenthixol acetate.
Heikkila 1981b	Allocation: not sated. Participants: people with schizophrenia, other psychosis. Interventions: oral cis (Z) -clopenthixol, oral haloperidol, placebo, not zuclopenthixol acetate.
Heikkila 1992	Allocation: randomised. Participants: people with acute or exacerbated chronic schizophrenia, paranoid states, paranoid reactive psychosis. Interventions: oral zuclopenthixol, oral haloperidol, not zuclopenthixol acetate.
Hicklin 1967	Allocation: open study, not stated to be randomised. Participants: mostly people with schizophrenia. Interventions: clopenthixol, clopenthixol and levomepromazine, reserpine, not zuclopenthixol acetate.
Huttunen 1994	Allocation: randomised. Participants: people with schizophrenia, schizophreniform disorder. Interventions: oral zuclopenthixol, oral risperidone, not zuclopenthixol acetate.
Karsten 1981	Allocation: randomised. Participants: people with oligophrenia. Interventions: oral haloperidol, zuclopenthixol or placebo, not zuclopenthixol acetate.

Study	Reason for exclusion
Kingstone 1970	Allocation: randomised. Participants: people with acute psychosis. Interventions: oral chlorpromazine, oral clopenthixol, not zuclopenthixol acetate.
Knegtering 2002	Allocation: not randomised.
Kordas 1968	Allocation: not stated. Participants: people with schizophrenia. Interventions: oral clopenthixol, oral chlorpromazine, not zuclopenthixol acetate.
Kristiansen 2001	Allocation: randomised. Participnats: healthy people, not people with schizophrenia.
Lehmann 1970	Allocation: not stated. Participants: people with schizophrenia. Interventions: oral thiothixene, oral chlorprothixene, oral clopenthixol, not zuclopenthixol acetate.
Lowert 1989	Allocation: not randomised, open clinical trial.
Loza 2001	Allocation: randomised. Participants: people with first episode of paranoid schizophrenia. Interventions: typical antipsychotics (zuclopenthixol, perphenazine, haloperidol or perazine), atypical (risperidone, olanzapine, quetiapine) antipsychotics, no specific reference to zuclopenthixol acetate.
Lublin 1991	Allocation: randomised. Participants: people with psychosis. Interventions: oral haloperidol, oral zuclopenthixol, not zuclopenthixol acetate.
Malt 1995	Allocation: randomised. Participants: people with mental retardation.
Meyers 1972	Allocation: not randomised, open clinical trial.
Moller 1994	Allocation: not randomised, open clinical trial.
Predescu 1991	Allocation: not randomised, open clinical trial.
Romain 1996	Allocation: not randomised, open study.
Saxena 1996	Alllocation: not clearly stated. Participants: people with chronic schizophrenia. Interventions: zuclopenthixol decanoate, fluphenazine decanoate, not zuclopenthixol acetate.
Schlosberg 1991	Allocation: not randomised, open pilot study.
Serafetinides 1971	Allocation: randomised. Participants: people with schizophrenia. Interventions: molindone, chlorpromazine, not zuclopenthixol acetate.
Serafetinides 1972	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral haloperidol, oral clopenthixol, oral chlorpromazine, placebo, not zuclopenthixol acetate.
Serafetinides 1973a	Allocation: double blind (four trials). Participants: people with schizophrenia.

Study	Reason for exclusion
	Interventions: one of the four trials compared clopenthixol with placebo, not zuclopenthixol acetate.
Serafetinides 1973b	Allocation: not randomised, correlational study.
Shelton 1969	Allocation: not clearly stated. Participants: people with schizophrenia. Interventions: clopenthixol, trifluperazine. Outcome: achilles reflex measurement.
Tan 1993	Allocation: not randomised, open clinical trial.
Weiser 1975	Allocation: not clearly stated. Participants: people with acute and subacute schizophrenia. Interventions: droperidol IV, clopenthixol IM, clozapine IM, not zuclopenthixol acetate.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Lamure 2003

Methods	Allocation: randomised, no further information. Blinding: none (open randomised multicentre controlled clinical trial). Design: parallel. Duration: 3 months. Consent: not mentioned.
Participants	Diagnosis: schizophrenia (DSM-III-R). History: acute exacerbation. N = 88. Age: 18 - 70. Sex: both men and women. Setting: hospital.
Interventions	1. Zuclopenthixol acetate IM: dose 50 to 150 mg every 48-72h. Once initial episode had stabilised, oral or depot zuclopenthixol acetate were given. 2. Haloperidol IM: dose 5 to 20 mg every 6 - 24h. Once initial episode has stabilised, oral or depot haloperidol were used.
Outcomes	Mental state: BPRS, CGI. Adverse effects: UKU. Duration of inpatient stay. Nursing time in minutes. Cost of the two treatment strategies for 90 day period.

Lamure 2003 *(Continued)*

Notes	The investigators were given a free choice of co-prescriptions, galenic form, duration of medication, duration of hospitalisation and methods for ambulatory management.

Mental state scales
BPRS - Brief Psychiatric Rating Scale
CGI - Clinical Global Impression

Adverse effects
UKU-SERS - UKU Side Effects Rating Scale

DATA AND ANALYSES

Comparison 1. ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE

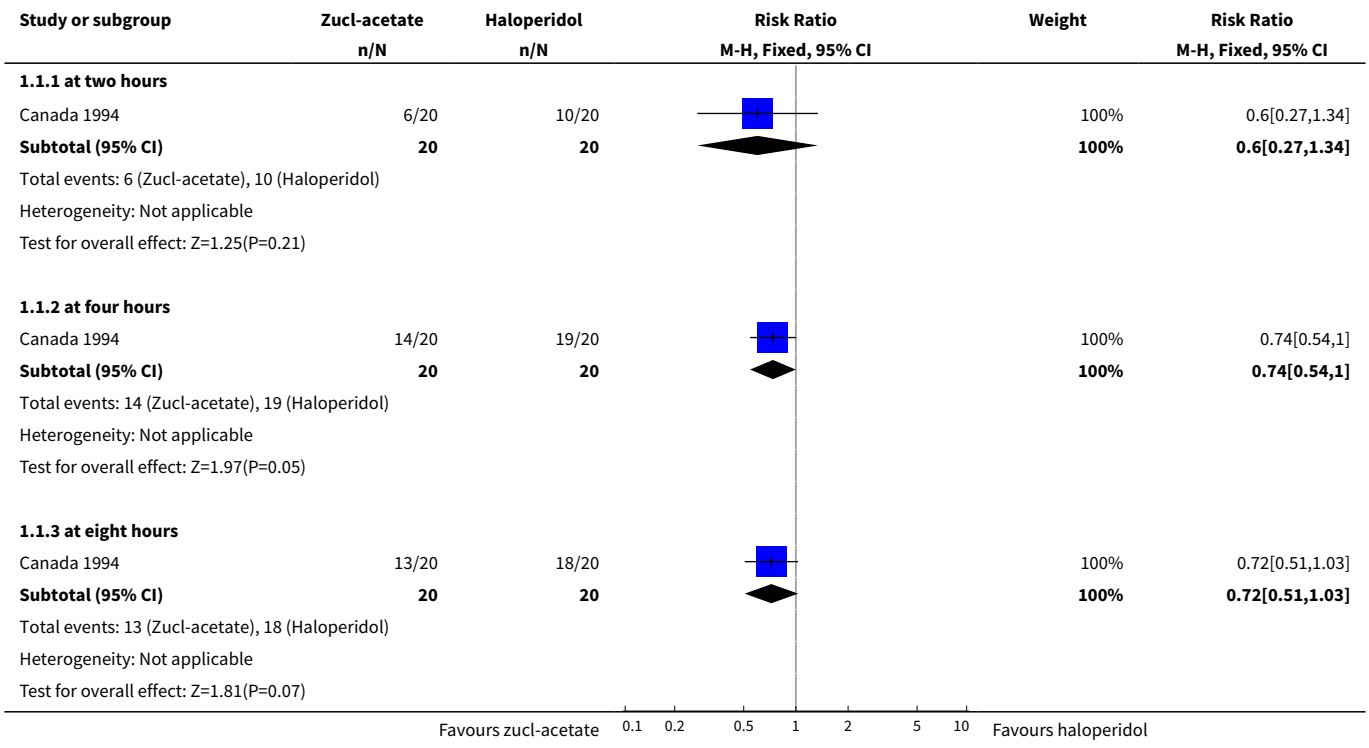
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sedation/tranquillisation: Not sedated	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 at two hours	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.27, 1.34]
1.2 at four hours	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.54, 1.00]
1.3 at eight hours	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.51, 1.03]
2 Global state: 1. Requiring supplementary medication	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 antipsychotics	3	134	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.97, 2.30]
2.2 benzodiazepines	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.03 [0.00, 0.47]
3 Global state: 2. Requiring 3 or more injections - over 7 days	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.18, 0.84]
4 Global state: 3. Average change - by day nine (CGI, high score = poor)	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.75, 0.65]
5 Behaviour: Average score (NOSIE, high score = best)	1	40	Mean Difference (IV, Fixed, 95% CI)	-4.82 [-10.46, 0.82]
6 Mental state: 1. No important improvement - by >36 hours	2	188	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.39, 1.86]
7 Mental state: 2. Average score (BPRS, high score = poor, data skewed)			Other data	No numeric data
8 Adverse effects: 1. Any adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 at 1 day	1	148	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.25, 1.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 at 3 days	1	148	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.56, 1.68]
8.3 at 6 days	1	148	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.43, 1.27]
9 Adverse effects: 2a. Movement disorders - binary outcomes	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 dystonia (spasmodic postural disorder) - by 24 hours	3	242	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.34, 1.36]
9.2 dystonia (spasmodic postural disorder) - by 48 hours	1	44	Risk Ratio (M-H, Fixed, 95% CI)	2.75 [0.12, 64.04]
9.3 hyperkinesia (elevation of activity) - by 6 days	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [0.18, 19.08]
9.4 dystonia (spasmodic postural disorder) - by 6 days	1	50	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [0.12, 65.08]
9.5 hyperkinesia (elevation of activity) - by 24 hours	2	198	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.32, 1.81]
9.6 dystonia (spasmodic postural disorder) - by 72 hours	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.06, 13.69]
9.7 hypokinesia (reduction in movement) - by 24 hours	3	242	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.19, 1.16]
9.8 hypokinesia (reduction in movement) - by 48 hours	1	44	Risk Ratio (M-H, Fixed, 95% CI)	6.42 [0.35, 117.34]
9.9 hypokinesia (reduction in movement) - by 72 hours	1	44	Risk Ratio (M-H, Fixed, 95% CI)	4.58 [0.23, 90.30]
9.10 hypokinesia (reduction in movement) - by 6 days	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.11 restlessness (motor akathisia) - by 24 hours	2	198	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [0.58, 4.59]
9.12 restlessness (motor akathisia) - by 6 days	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.13 rigidity - by 24 hours	3	242	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.37, 1.20]
9.14 rigidity - by 48 hours	1	44	Risk Ratio (M-H, Fixed, 95% CI)	2.75 [0.12, 64.04]
9.15 rigidity - by 72 hours	1	44	Risk Ratio (M-H, Fixed, 95% CI)	2.74 [0.31, 24.34]
9.16 rigidity - by 6 days	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [0.18, 19.08]
9.17 tremor - by 24 hours	3	242	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.33, 1.50]
9.18 tremor - by 48 hours	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.04, 4.68]

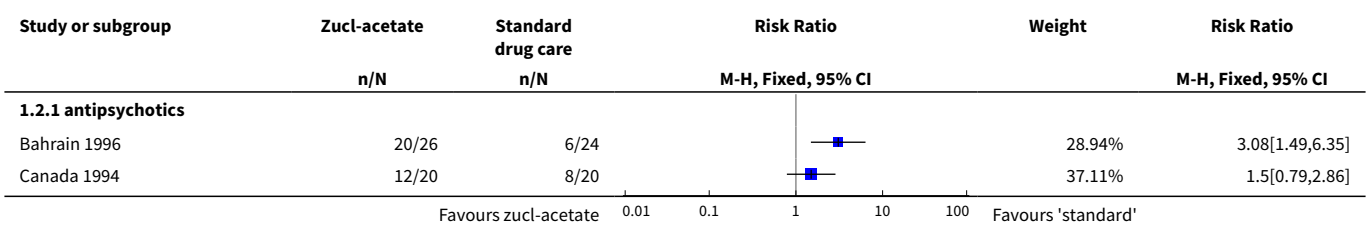
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.19 tremor - by 72 hours	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.06, 13.69]
9.20 tremor - by 6-7 days	2	120	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.08, 1.00]
9.21 use of antiparkinsonian medication	4	276	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.80, 1.15]
10 Adverse effects: 2b. Movement disorders - continuous outcomes (data skewed)			Other data	No numeric data
10.1 dyskinesia (non-postural involuntary movements) - average total score (CGI, high score = poor)			Other data	No numeric data
10.2 dyskinesia (non-postural involuntary movements) - average total score (ESRS, high score = poor)			Other data	No numeric data
10.3 dystonia (spasmodic postural disorder) - average total score (ESRS, high score = poor)			Other data	No numeric data
10.4 parkinsonism - average severity score (CGI. high score = poor)			Other data	No numeric data
10.5 parkinsonism - average total score (ESRS, high score = poor)			Other data	No numeric data
11 Adverse effects: 3. Other specific effects	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 dry mouth/blurred vision - by 24 hours	2	192	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.48, 1.70]
11.2 dry mouth/ blurred vision - by 48 hours	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.18, 18.70]
11.3 dry mouth/ blurred vision - by 72 hours	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.18, 18.70]
11.4 dry mouth/ blurred vision - by 6 days	1	38	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [0.45, 9.16]
11.5 dizziness - by 24 hours	2	192	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.46, 2.88]
11.6 dizziness - by 48 hours	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.06, 13.69]
11.7 dizziness - by 72 hours	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.06, 13.69]
11.8 hypotension, severe - by 24 hours	1	50	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [0.12, 65.08]
11.9 reaction at injection site - time not specified	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.01, 6.69]

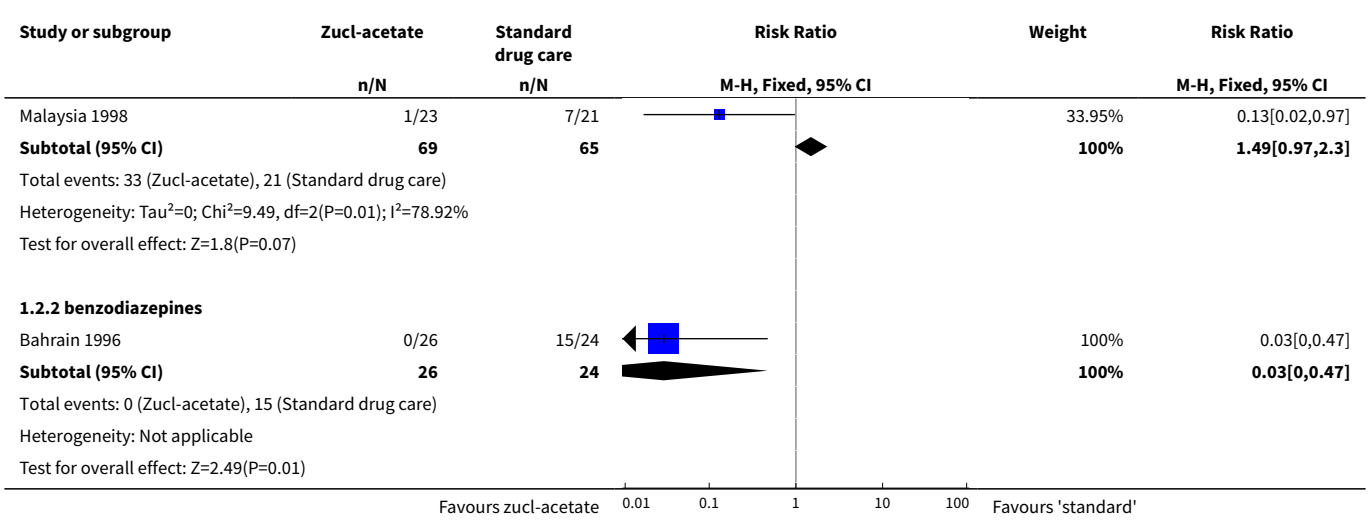
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
11.10 palpitations - by 6 days	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.34, 7.80]
11.11 salivation, excessive - by 24 hours	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.12]
11.12 salivation, excessive - by 48 hours	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 3.61]
12 Leaving study early	8	522	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.31, 2.31]

Analysis 1.1. Comparison 1 ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE, Outcome 1 Sedation/tranquillisation: Not sedated.

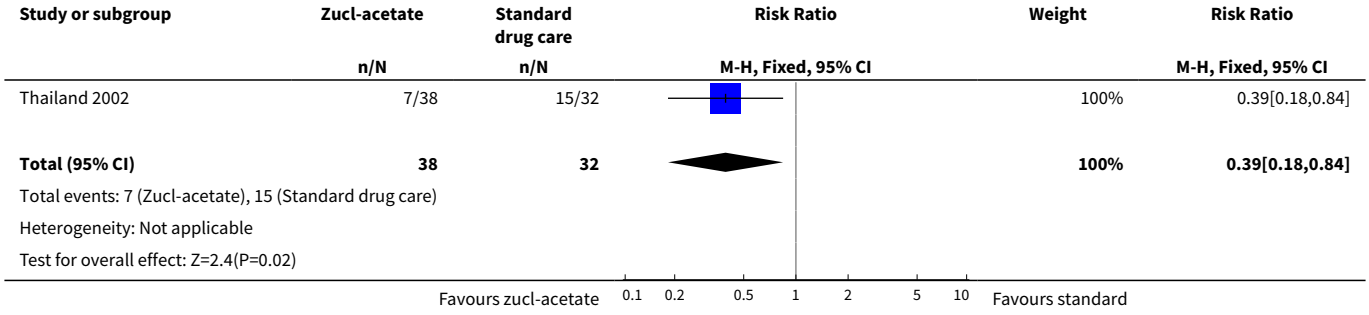


Analysis 1.2. Comparison 1 ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE, Outcome 2 Global state: 1. Requiring supplementary medication.

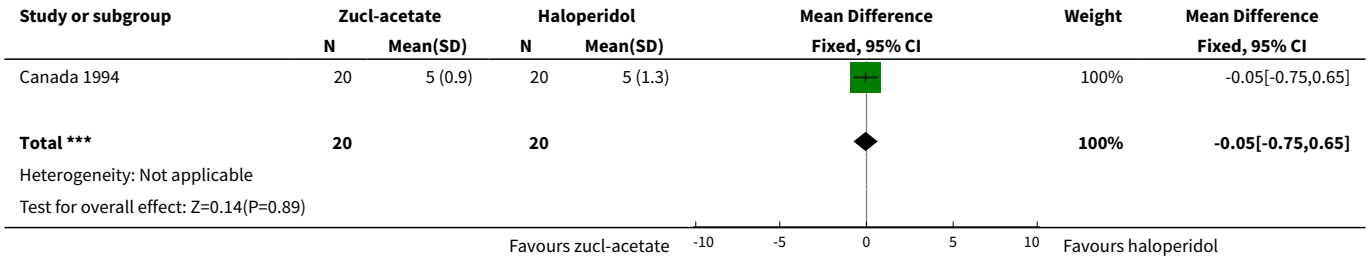




Analysis 1.3. Comparison 1 ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE, Outcome 3 Global state: 2. Requiring 3 or more injections - over 7 days.

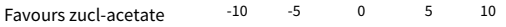


Analysis 1.4. Comparison 1 ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE, Outcome 4 Global state: 3. Average change - by day nine (CGI, high score = poor).



Analysis 1.5. Comparison 1 ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE, Outcome 5 Behaviour: Average score (NOSIE, high score = best).

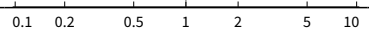
Study or subgroup	Zucl-acetate N	Zucl-acetate Mean(SD)	Haloperidol N	Haloperidol Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Canada 1994	20	176.9 (9)	20	181.7 (9.3)		100%	-4.82[-10.46,0.82]
Total ***	**20**		**20**			**100%**	**-4.82[-10.46,0.82]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.67(P=0.09)							



Favours zucl-acetate — Favours haloperidol

Analysis 1.6. Comparison 1 ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE, Outcome 6 Mental state: 1. No important improvement - by >36 hours.

Study or subgroup	Zucl-acetate n/N	Standard drug care n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Canada 1994	4/20	4/20		33.75%	1[0.29,3.45]
Nordic 1993	7/83	7/65		66.25%	0.78[0.29,2.12]
Total (95% CI)	**103**	**85**		**100%**	**0.86[0.39,1.86]**
Total events: 11 (Zucl-acetate), 11 (Standard drug care)					
Heterogeneity: Tau^2=0; Chi^2=0.09, df=1(P=0.76); I^2=0%					
Test for overall effect: Z=0.39(P=0.7)					



Favours zucl-acetate — Favours 'standard'

Analysis 1.7. Comparison 1 ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE, Outcome 7 Mental state: 2. Average score (BPRS, high score = poor, data skewed).

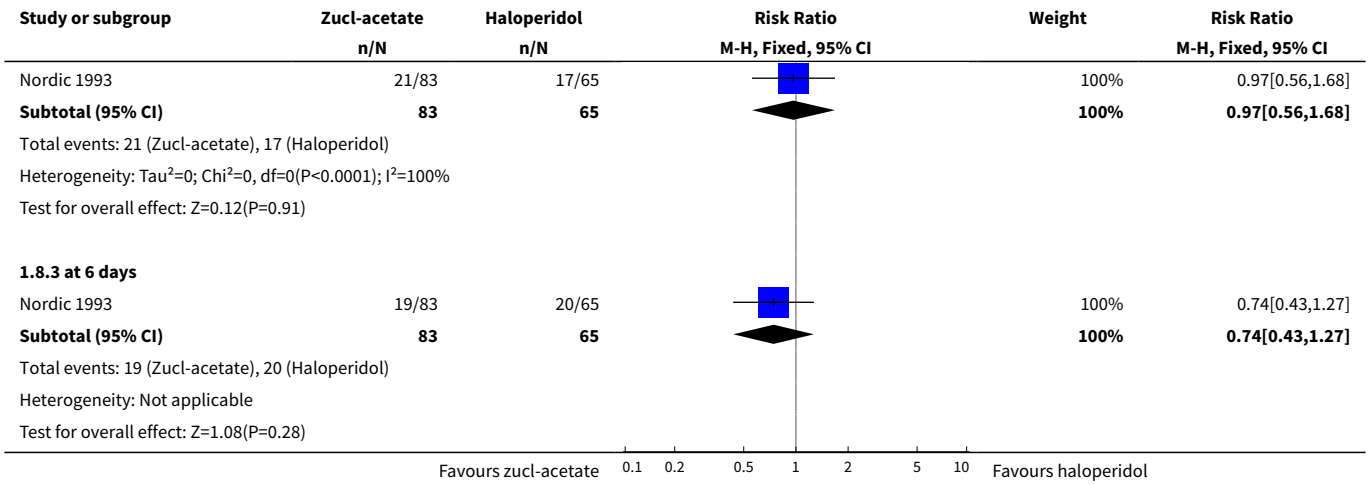
Mental state: 2. Average score (BPRS, high score = poor, data skewed)

Study	Intervention	Mean score	SD	N
Canada 1994	Zuclopentixol acetate	25.65	10.01	20
Canada 1994	Haloperidol	26.55	15.1	20

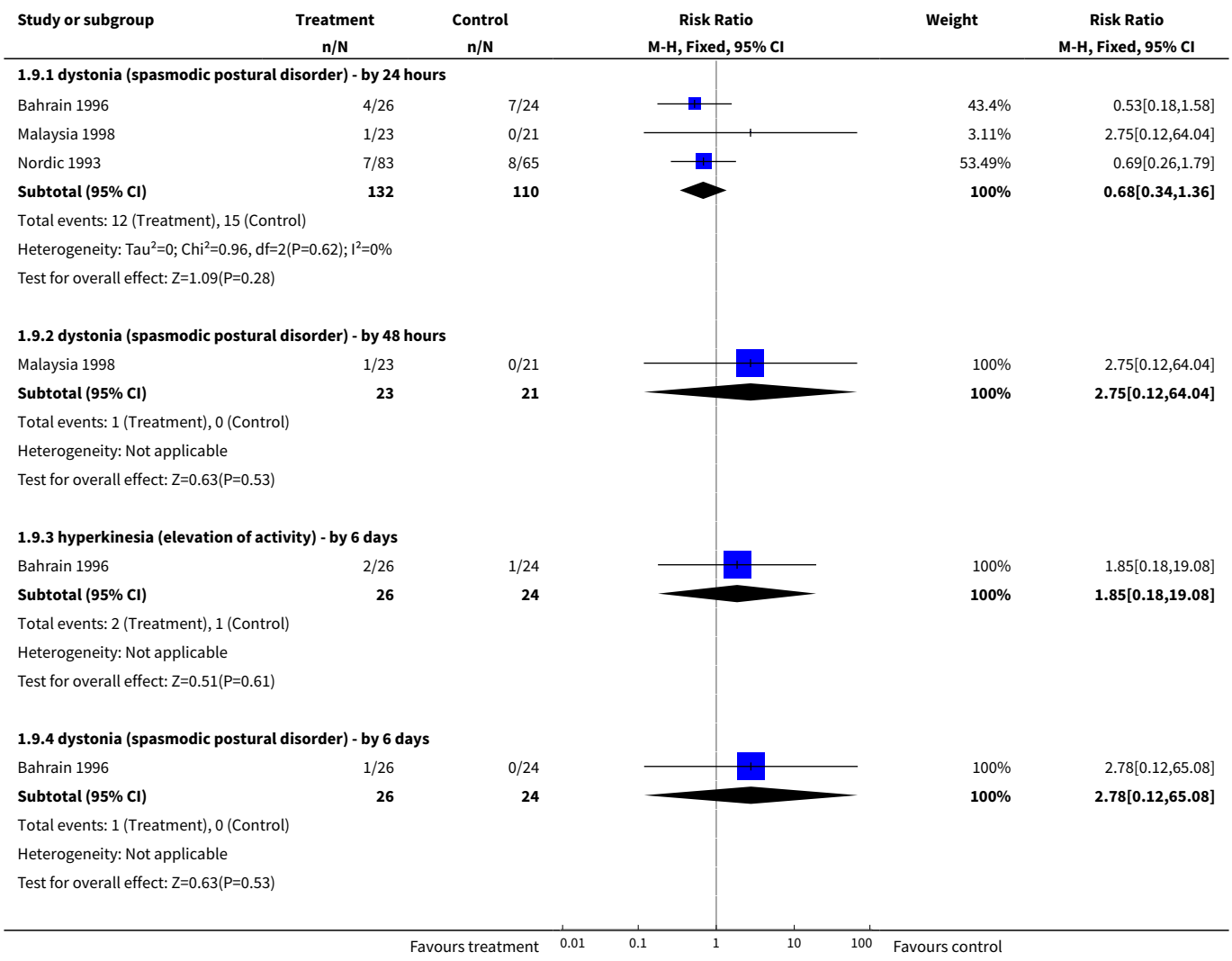
Analysis 1.8. Comparison 1 ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE, Outcome 8 Adverse effects: 1. Any adverse effects.

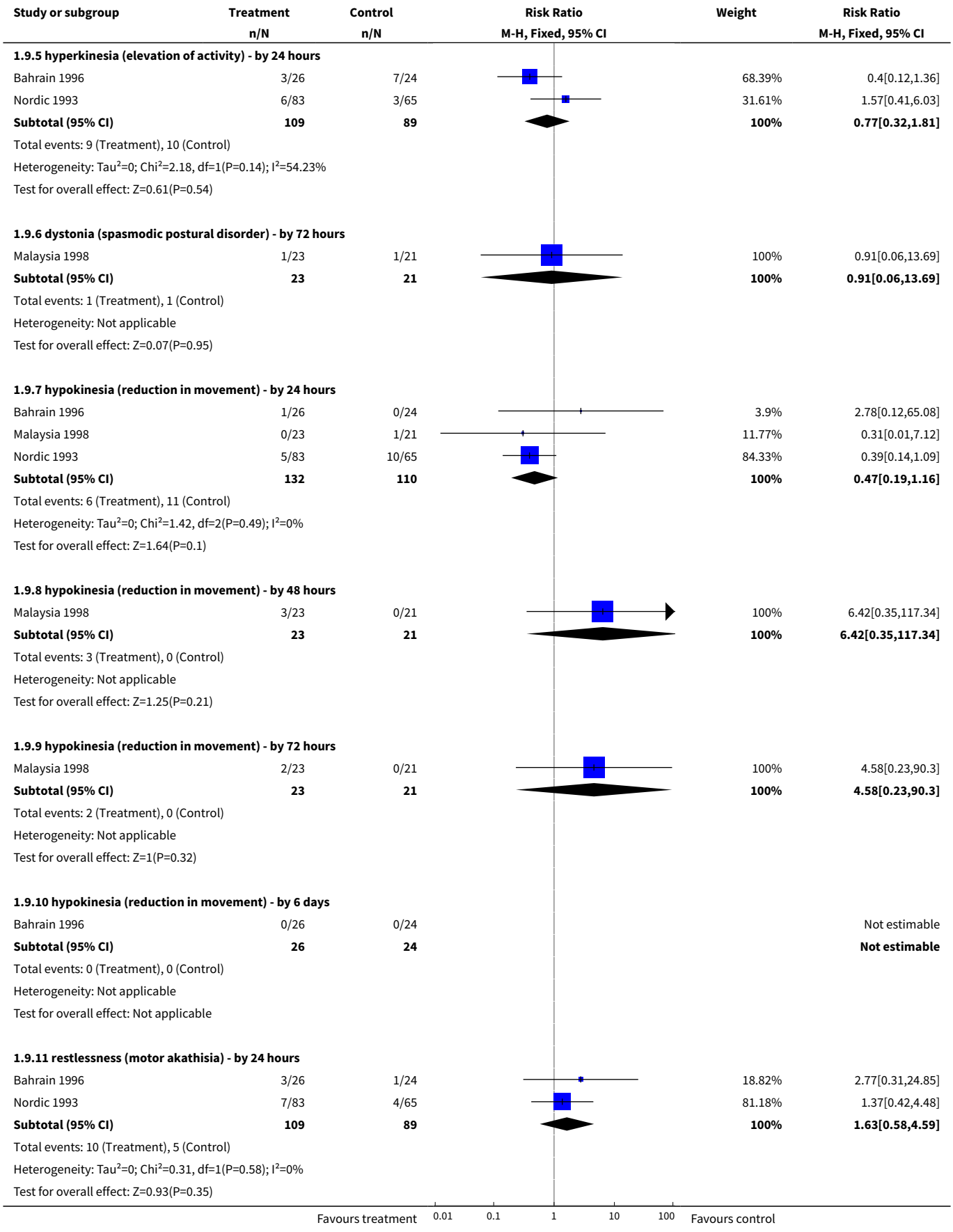
Study or subgroup	Zucl-acetate n/N	Haloperidol n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 at 1 day					
Nordic 1993	9/83	13/65		100%	0.54[0.25,1.19]
Subtotal (95% CI)	**83**	**65**		**100%**	**0.54[0.25,1.19]**
Total events: 9 (Zucl-acetate), 13 (Haloperidol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.53(P=0.13)					
1.8.2 at 3 days					

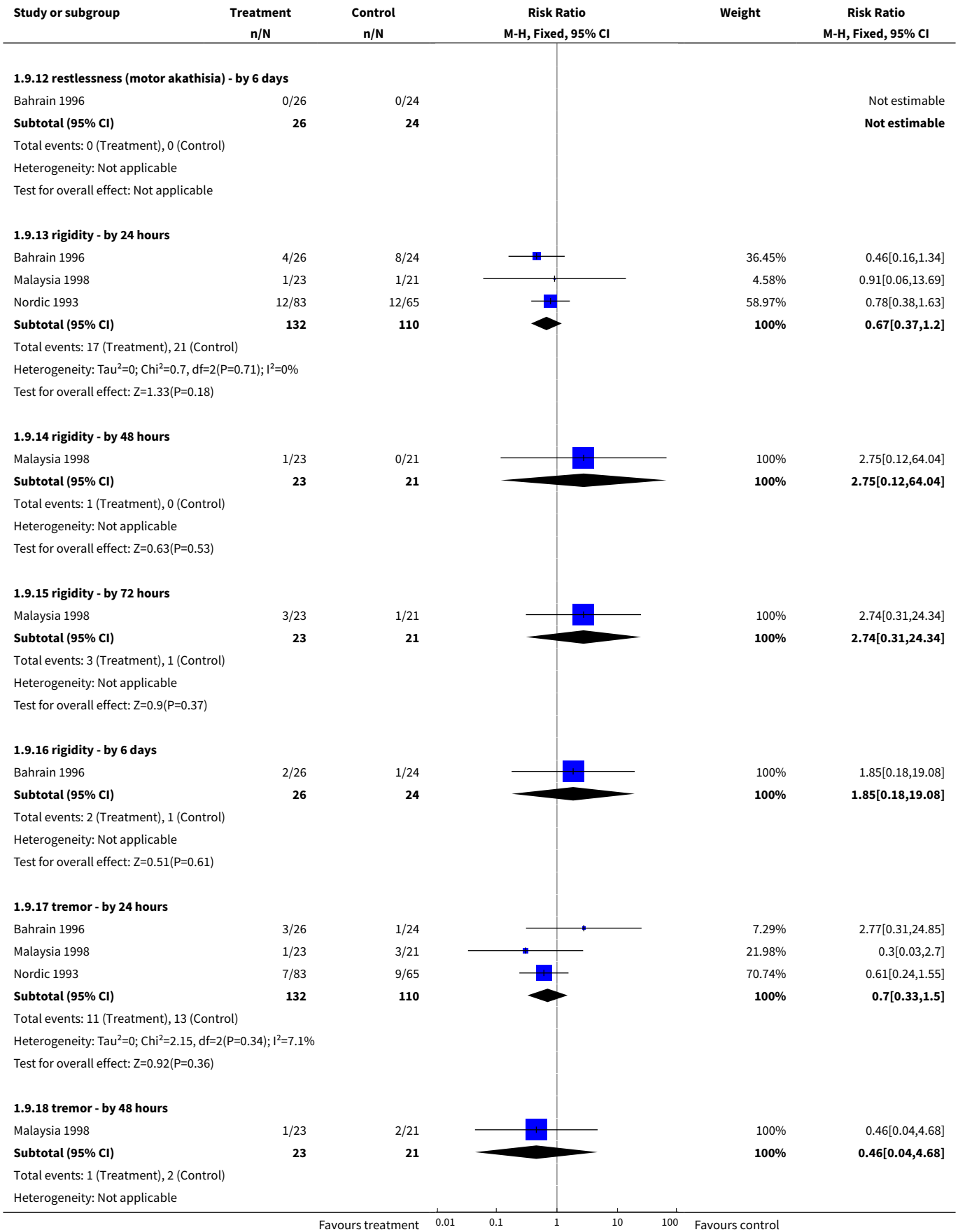
Favours zucl-acetate — Favours haloperidol

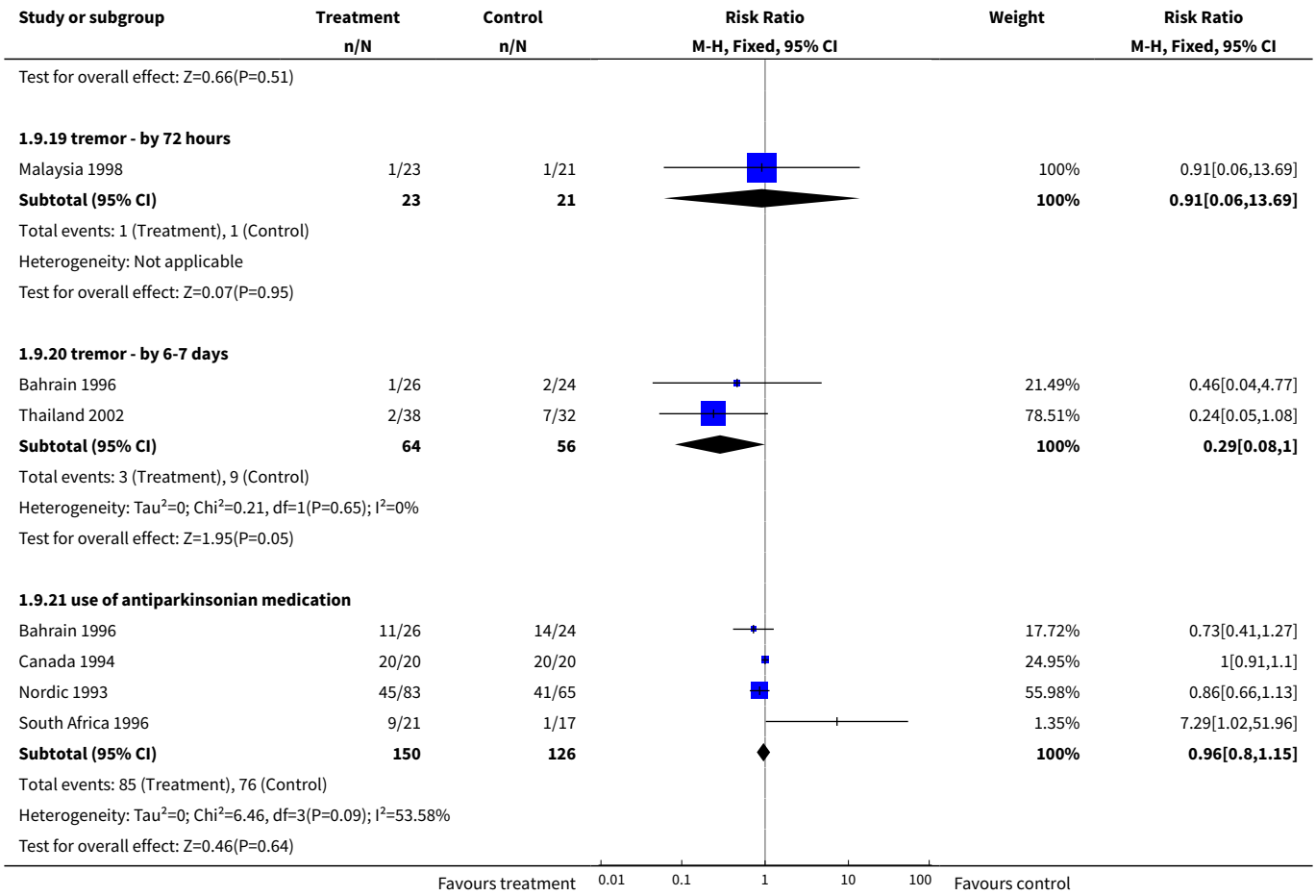


Analysis 1.9. Comparison 1 ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE, Outcome 9 Adverse effects: 2a. Movement disorders - binary outcomes.









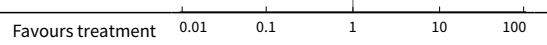
Analysis 1.10. Comparison 1 ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE, Outcome 10 Adverse effects: 2b. Movement disorders - continuous outcomes (data skewed).

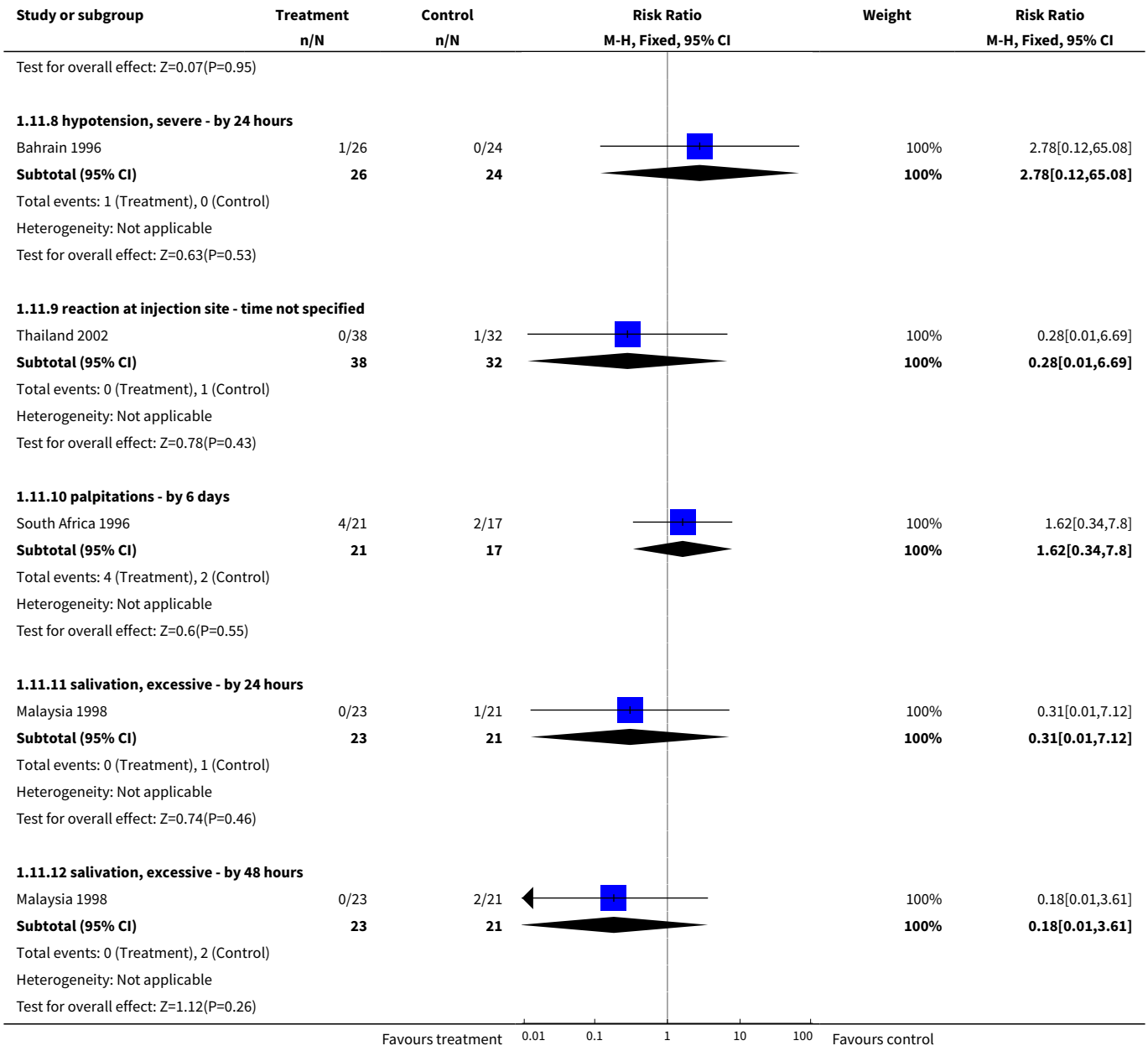
Adverse effects: 2b. Movement disorders - continuous outcomes (data skewed)

Study	Intervention	Mean	SD	N	Notes
dyskinesia (non-postural involuntary movements) - average total score (CGI, high score = poor)					
Canada 1994	Zuclopentixol acetate	1.40	1.35	20	
Canada 1994	Haloperidol	0.95	1.43	20	
dyskinesia (non-postural involuntary movements) - average total score (ESRS, high score = poor)					
Canada 1994	Zuclopentixol acetate	2.05	2.44	20	
Canada 1994	Haloperidol	1.65	2.96	20	
dystonia (spasmodic postural disorder) - average total score (ESRS, high score = poor)					
Canada 1994	Zuclopentixol acetate	0.60	1.10	20	
Canada 1994	Haloperidol	0.70	1.13	20	
parkinsonism - average severity score (CGI. high score = poor)					
Canada 1994	Zuclopentixol acetate	3.45	1.00	20	
Canada 1994	Haloperidol	3.00	1.17	20	
parkinsonism - average total score (ESRS, high score = poor)					
Canada 1994	Zuclopentixol acetate	13.20	6.08	20	
Canada 1994	Haloperidol	10.40	5.99	20	

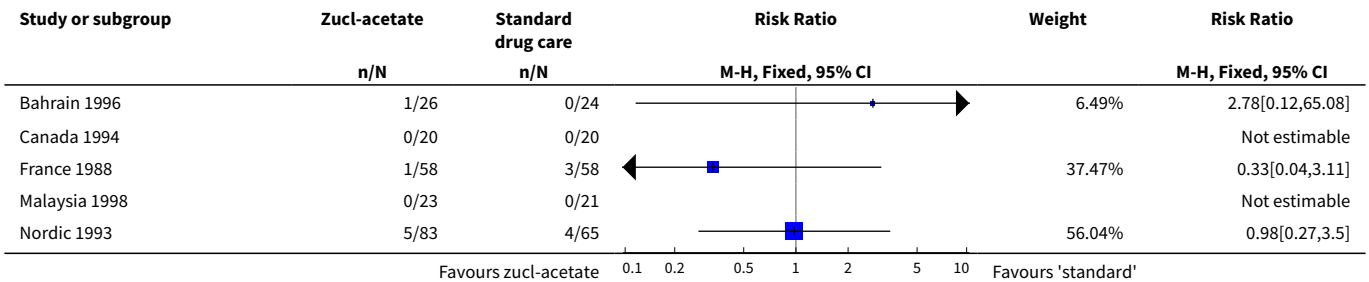
Analysis 1.11. Comparison 1 ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE, Outcome 11 Adverse effects: 3. Other specific effects.

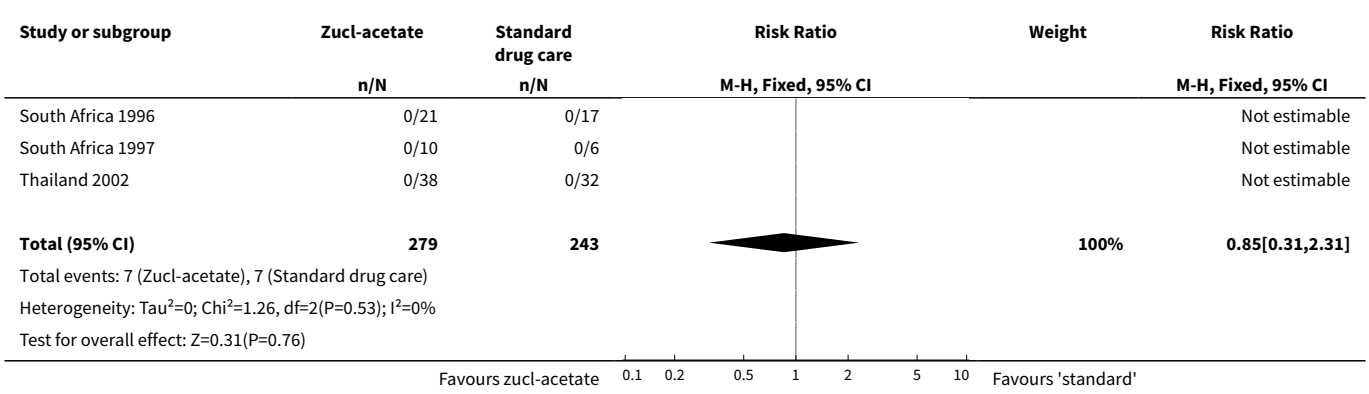
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 dry mouth/blurred vision - by 24 hours					
Malaysia 1998	1/23	0/21		3.22%	2.75[0.12,64.04]
Nordic 1993	15/83	14/65		96.78%	0.84[0.44,1.61]
Subtotal (95% CI)	**106**	**86**		**100%**	**0.9[0.48,1.7]**
Total events: 16 (Treatment), 14 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.53, df=1(P=0.47); I^2=0%					
Test for overall effect: Z=0.32(P=0.75)					
1.11.2 dry mouth/ blurred vision - by 48 hours					
Malaysia 1998	2/23	1/21		100%	1.83[0.18,18.7]
Subtotal (95% CI)	**23**	**21**		**100%**	**1.83[0.18,18.7]**
Total events: 2 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.51(P=0.61)					
1.11.3 dry mouth/ blurred vision - by 72 hours					
Malaysia 1998	2/23	1/21		100%	1.83[0.18,18.7]
Subtotal (95% CI)	**23**	**21**		**100%**	**1.83[0.18,18.7]**
Total events: 2 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.51(P=0.61)					
1.11.4 dry mouth/ blurred vision - by 6 days					
South Africa 1996	5/21	2/17		100%	2.02[0.45,9.16]
Subtotal (95% CI)	**21**	**17**		**100%**	**2.02[0.45,9.16]**
Total events: 5 (Treatment), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.92(P=0.36)					
1.11.5 dizziness - by 24 hours					
Malaysia 1998	2/23	1/21		13.45%	1.83[0.18,18.7]
Nordic 1993	8/83	6/65		86.55%	1.04[0.38,2.86]
Subtotal (95% CI)	**106**	**86**		**100%**	**1.15[0.46,2.88]**
Total events: 10 (Treatment), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.19, df=1(P=0.67); I^2=0%					
Test for overall effect: Z=0.3(P=0.77)					
1.11.6 dizziness - by 48 hours					
Malaysia 1998	1/23	1/21		100%	0.91[0.06,13.69]
Subtotal (95% CI)	**23**	**21**		**100%**	**0.91[0.06,13.69]**
Total events: 1 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.07(P=0.95)					
1.11.7 dizziness - by 72 hours					
Malaysia 1998	1/23	1/21		100%	0.91[0.06,13.69]
Subtotal (95% CI)	**23**	**21**		**100%**	**0.91[0.06,13.69]**
Total events: 1 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					





Analysis 1.12. Comparison 1 ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE, Outcome 12 Leaving study early.

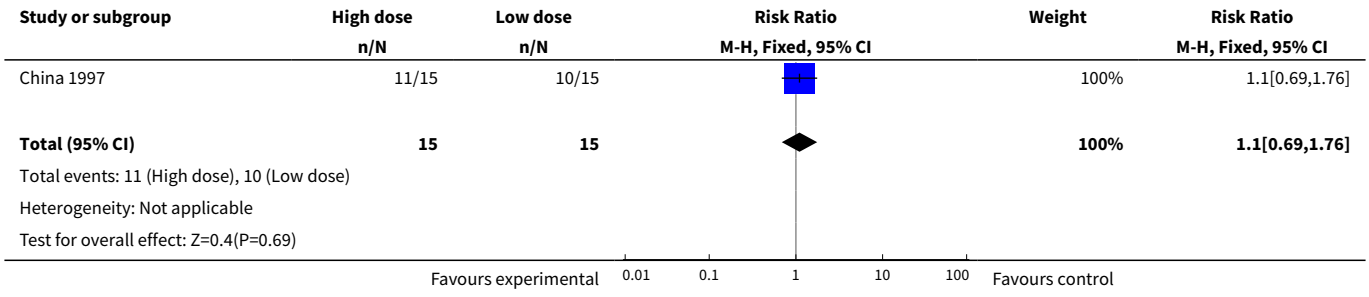




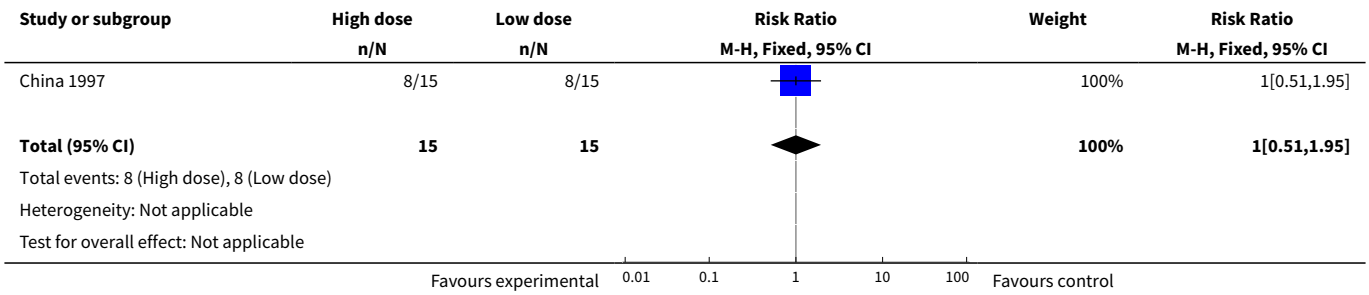
Comparison 2. ZUCLOPENTHIXOL ACETATE (HIGH DOSE) vs ZUCLOPENTHIXOL ACETATE (LOW DOSE)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state:1.Not recovered (BPRS, <80% decrease in BPRS score)	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.69, 1.76]
2 Mental state:2.Not markedly improved (BPRS, < 60% decrease in BPRS score)	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.51, 1.95]
3 Mental state:3. Not improved (BPRS, <30% decrease in BPRS score)	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.17, 2.07]
4 Adverse effects:1. Extrapiramidal side effects (TESS)	1	30	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.74, 7.35]

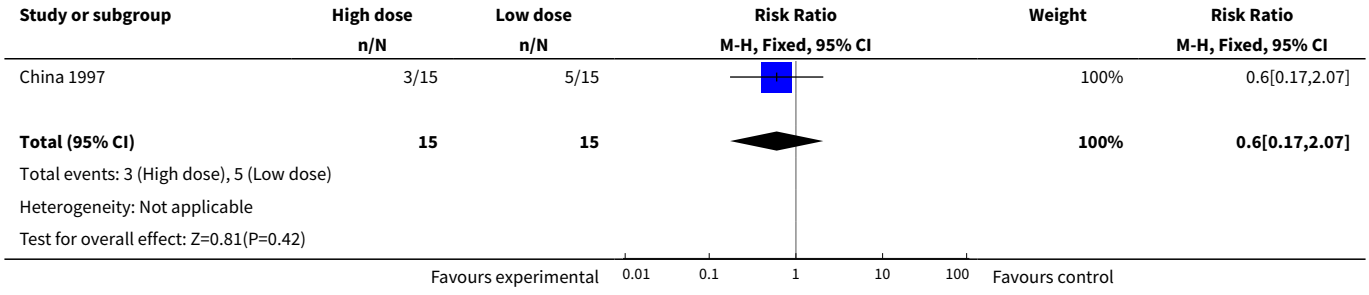
Analysis 2.1. Comparison 2 ZUCLOPENTHIXOL ACETATE (HIGH DOSE) vs ZUCLOPENTHIXOL ACETATE (LOW DOSE), Outcome 1 Mental state:1.Not recovered (BPRS, <80% decrease in BPRS score).



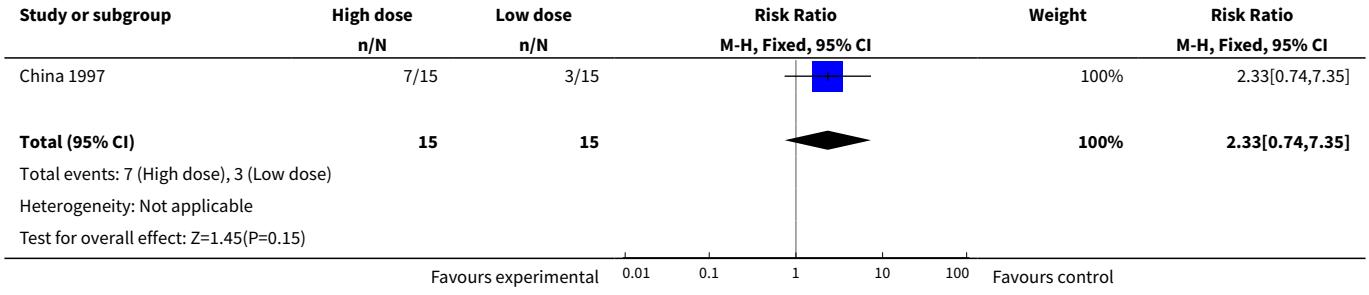
Analysis 2.2. Comparison 2 ZUCLOPENTHIXOL ACETATE (HIGH DOSE) vs ZUCLOPENTHIXOL ACETATE (LOW DOSE), Outcome 2 Mental state:2.Not markedly improved (BPRS, < 60% decrease in BPRS score).



Analysis 2.3. Comparison 2 ZUCLOPENTHIXOL ACETATE (HIGH DOSE) vs ZUCLOPENTHIXOL ACETATE (LOW DOSE), Outcome 3 Mental state:3. Not improved (BPRS, <30% decrease in BPRS score).



Analysis 2.4. Comparison 2 ZUCLOPENTHIXOL ACETATE (HIGH DOSE) vs ZUCLOPENTHIXOL ACETATE (LOW DOSE), Outcome 4 Adverse effects:1. Extrapiramidal side effects (TESS).



ADDITIONAL TABLES

Table 1. Reviews focusing on similar participant groups

Focus of Review	Reference
Aripiprazole for psychosis-induced agitation/aggression	Pagadala 2009
Benzodiazepines for psychosis-induced agitation/aggression	Gillies 2005

Table 1. Reviews focusing on similar participant groups *(Continued)*

Benzodiazepines for schizophrenia	Volz 2007
Containment strategies for psychosis-induced agitation/aggression	Muralidharan 2006
Chlorpromazine for psychosis-induced agitation/aggression	Ahmed 2010
Haloperidol (rapid tranquillisation) for psychosis-induced agitation/aggression	Powney 2011
Haloperidol for people with schizophrenia and chronic aggression	Khushu 2012 (to be published 2012)
Haloperidol + promethazine for psychosis-induced agitation/aggression	Huf 2009
Loxapine for schizophrenia	Chakrabarti 2007
Loxapine inhaler for psychosis-induced agitation/aggression	Vangala 2012 (to be published 2012)
Olanzapine IM for psychosis-induced agitation/aggression	Belgamwar 2005
Quetiapine for psychosis induced aggression or agitation	Wilkie 2012 (to be published 2012)
Risperidone for psychosis-induced agitation/aggression	Ahmed 2011
Seclusion and restraint for psychosis-induced agitation/aggression	Sailas 2000

Table 2. Suggested design of study

Methods	Allocation: randomised, explicit sequence generation and allocation concealment. Blinding: double, described and tested. Setting: inpatient and community. Duration: 36 hours at least.
Participants	Diagnosis: schizophrenia or similar serious mental illness involving psychotic symptoms (diagnosed using a well established diagnostic criteria). N = 300.* Age: all age. Sex: both. History: any.
Interventions	1. Zuclopenthixol acetate: any dose. N = 150. 2. Any other drug intervention. N = 150.
Outcomes	Behaviour: tranquillisation (feeling of calmness and/or calm, non-sedated behaviour). Adverse effects: general and specific. Service outcome: days in hospital. Global state: CGI. Mental state: BPRS and PANSS. Economic outcomes: cost benefit, cost utility.

Table 2. Suggested design of study *(Continued)*

	Quality of life: QOL scale.
Notes	* For adequate power to detect 20% difference in binary outcome between groups.

Mental state scales
BPRS - Brief Psychiatric Rating Scale
CGI - Clinical Global Impression
PANSS - Positive and Negative Syndrome Scale

APPENDICES

Appendix 1. Previous search strategy

1. Search strategy prior to 2011
1.1 Abstracts of congresses on CD-ROM
C.I.N.P. Congress, Melbourne, Australia (1996)
World Congress of Psychiatry, Madrid, Spain (1996)
9th ECNP Congress, Amsterdam, Netherlands (1996)
8th Congress of Association of European Psychiatrists, London UK (1996)
The CONFER CD versions of these conference proceedings were searched using the following terms:

zuclopenthixol or zuclopenthixol acetate or clopenthixol or clopixol or acuphase

1.2 ClinicalTrials.gov (http://www.clinicaltrials.gov - accessed 5.10.2000) was searched using the following phrase

[zuclopenthixol]

1.3 The Cochrane Library (1997, CD-ROM, issue 2) was searched using the phrase:

[zuclopenthixol or 0-108 or clopenthixol or clopixol or <ME> clopenthixol]

1.4 MEDLINE (to June 1997) was methodically searched using the phrase:

(clopenthixol/ all subheadings in MeSH) or clopenthixol or zuclopenthixol or acuphase or acutard or clopixol or (short-* near (depot* or neuroleptic* or antipsychotic*))

All MEDLINE citations were then hand searched for studies likely to be relevant. In order to evaluate the efficacy of the 'Filter' produced by the Nordic Cochrane Centre (ftp://ftp.cochrane.co.uk/pub/tools), citations were selected using combinations of the three filters in serial and in parallel. The second strategy is supposed to increase the sensitivity of the searching process, although making it less precise (lower specificity).

1.5 MetaRegister of Controlled Trials (http://www.controlled-trials.com - accessed 5.10.2000) was searched with the following phrase:

[zuclopenthixol]

1.6 National Institutes of Health (NIH) Clinical Research Studies Register (http://clinicalstudies.info.nih.gov/index.html - accessed 5.10.2000) was searched using the phrase:

[zuclopenthixol]

1.7 National Research Register (Issue 3, 2000) was searched using the Cochrane Schizophrenia Group's phrase for schizophrenia (see Group search strategy) combined with the phrase:

[zuclopenthixol]

Appendix 2. Previous data collection and analysis

1. Selection of trials

Two reviewers inspected all citations independently identified (MF, EC). When disputes arose as to which category a citation should be allocated, resolution was attempted by discussion. When this was not possible the full article was acquired. All articles identified in this way were inspected by two reviewers, again independently (MF, EC). When disputes arose as to whether an article was indeed relevant to

this review, resolution was attempted by discussion. When this was not possible one further reviewer (CC) was asked to read the article and decide. CC was sent 10% of the citations and articles included and excluded by EC and MF in order to check the use of inclusion criteria. Finally, where resolution was not possible because further information was necessary, data were not entered and the trial was allocated to the list of those awaiting assessment. Attempts were then made to contact authors in order to obtain further clarification of data.

For the 2003 update of the review, two reviewers (RG, MF) independently inspected all studies generated from the new search in their complete form where available. The studies were rated as for inclusion, for exclusion or for further evaluation based on their satisfaction of the inclusion criteria. Where reviewers agreed on the categorisation, the studies were included or excluded accordingly. Cases initially rated as for further evaluation were revisited until each reviewer had determined a final categorisation. Where there was disagreement regarding the suitability of studies for the update, consensus was initially attempted by discussion. If consensus was not reached, a third reviewer was asked to decide.

2. Assessment of methodological quality

Trials were allocated to the three categories described in the Cochrane Collaboration Handbook (Clarke 2003). Only trials that were stated to be randomised (categories A or B of the handbook) were included in this review. When disputes arose as to which category a trial should be allocated, resolution was attempted by discussion. When this was not possible because further information was necessary, data were not entered and the trial was allocated to the list of those awaiting assessment. Reviewers were not blinded to the names of the authors, institutions, journals of publication or results of the trials.

3. Addressing publication bias

Where possible, data from all identified and selected trials were to be entered into a funnel graph (size versus effect) in an attempt to detect the possibility of publication bias. It was hoped, for primary outcomes where there was a 'positive' effect of zuclopenthixol acetate, to calculate a fail-safe 'N'. This is the number of 'negative' studies that would be needed to reverse a conclusion that a significant relationship exists.

4. Data extraction

Data from the selected trials were extracted independently by EC and MF (RG and MF for the 2004 update). Again disputes were resolved by discussion. Trials were put into a list of those awaiting assessment when it was not possible to extract data or where further information was needed, and attempts were made to contact the authors.

5. Data synthesis

Data for 'non-standard' care were to be analysed separately from data for 'standard' care.

5.1 Binary data
We estimated the relative risk (RR) and the 95% Confidence Interval (CI). Where possible, we calculated the number need to treat (NNT). Where loss to follow up was greater than 20%, we did not use data because these reviewers (MF, EC, RG, CC) feel that, for such short term studies, this degree of loss was indicative of poor study quality.

5.2 Continuous data
We combined means from each study using weights based on their variances. Where possible, we estimated an 'effect size' measure expressing the mean difference as a multiple of the control standard deviation. Again, considering that zuclopenthixol acetate is a drug intended for short-term use, we decided that where data on 20% or more of people were lost, these should not be included in the analysis.

5.2.1 Skewed data
Mental health continuous data are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data we applied the following standards to all data before inclusion: (a) standard deviations and means were reported in the paper or were obtainable from the authors; (b) the standard deviation, when multiplied by two, was less than the mean (as otherwise the mean was unlikely to be an appropriate measure of the centre of the distribution (Altman 1996). Data which did not meet the second standard, were not entered on the RevMan software for graphical presentation as this assumes a normal distribution. Data not meeting these standards were reported in the 'other' data type tables.

5.3 Scales
For outcome instruments the minimum standards are that: (a) the psychometric properties of the instrument should have been described in a peer-reviewed journal; (b) the instrument should either be a self report, or completed by an independent rater or relative (not the therapist); and (c) the instrument should be a global assessment of an area of functioning.

5.4 Cluster trials
Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby p values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997, Gulliford 1999). Secondly, RevMan does not currently support meta-analytic pooling of clustered

dichotomous data, even when these are correctly analysed by the authors of primary studies, since the 'design effect' (a statistical correction for clustering) cannot be incorporated.

Where clustering was not accounted for in primary studies, we presented the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. Subsequent versions of this review will seek to contact first authors of studies to seek intra-class correlation co-efficients of their clustered data and to adjust for this using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, then we will also present these data as if from a non-cluster randomised study, but adjusted for the clustering effect.

We have sought statistical advice from the MRC Biostatistics Unit, Cambridge, UK. Dr Julian Higgins advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intraclass correlation co-efficent (ICC) [Design effect=1+(m-1)*ICC]. Should the ICC not be reported it was assumed to be 0.1 (Ukoumunne 1999).

If cluster studies had been appropriately analysed taking into account intra-class correlation coefficients and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.

6. Test for inconsistency

Firstly, consideration of all the included studies within any comparison was undertaken to estimate clinical heterogeneity. Then visual inspection of graphs was used to investigate the possibility of statistical heterogeneity. This was supplemented employing, primarily, the I-squared statistic. This provides an estimate of the percentage of inconsistency thought to be due to chance. Where the I-squared estimate was greater than or equal to 75%, this was interpreted as indicating the presence of high levels of heterogeneity (Higgins 2003). If inconsistency was high, data were not summated, but were presented separately and reasons for heterogeneity investigated.

WHAT'S NEW

Date	Event	Description
15 January 2013	Amended	Amendment of text: repetition of some text in methods section removed.

HISTORY

Review first published: Issue 4, 1997

Date	Event	Description
8 February 2012	New citation required but conclusions have not changed	Substantial update, conclusions not changed.
19 July 2011	New search has been performed	One new trial added (China 1997) and another study (Lamure 2003) is awaiting assessment.
5 October 2005	New citation required and minor changes	New studies sought but none found
8 May 2004	New citation required and conclusions have changed	Substantive amendment
14 February 2003	New citation required but conclusions have not changed	Three new trials have been added to the update - Bahrain 1996 (n=50), Malaysia 1998 (n=44) and Thailand 2002 (n=70).
17 May 2001	Amended	New studies sought but none included/excluded
15 July 1999	Amended	Reformatted

CONTRIBUTIONS OF AUTHORS

Kaushadh Jayakody - organised 2011 update, searching, study selection, data extraction, updating and re-drafting the text.

Ajit Kumar - study selection for 2011 update, data extraction and updating the review.

Roger Gibson - organised 2003 update, helped with searches, data extraction and re-drafting of the all text.

Shalmini Gunadasa - Data analysis and statistical expertise.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- South Warwickshire Mental Health Services, Warwick, UK.
- University of the State of Rio de Janeiro, Brazil.
- Oswaldo Cruz Foundation, Brazil.

External sources

- ARIF, University of Birmingham, UK.
- CNPq (Brazilian National Council of Research), Brazil.
- Warwickshire Health Authority, UK.
- University of Leeds, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This 2011 update does modify the protocol of the past which is reproduced in Appendix 1 and Appendix 2. Although developed and improved we do not think that the new protocol does materially change the approach of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Aggression [*drug effects]; Antipsychotic Agents [*therapeutic use]; Benzodiazepines [therapeutic use]; Clopenthixol [*therapeutic use]; Dibenzothiazepines [therapeutic use]; Haloperidol [therapeutic use]; Psychotic Disorders [*drug therapy]; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy]; Violence [psychology]

MeSH check words

Humans